INFLAMMATION

Dr. PRIYANKA SACHDEV, MD

Scan or Click to watch Cell Adaptation & Injury

Scan or Click to watch Apoptosis & Necrosis

Scan or Click to watch Inflammation

Scan or Click to watch Haemodynamic Disorder

Inflammation

- Inflammation is defined as the **local response of living mammalian tissues to injury from any agent**

Inflammation is distinct from infection

- **Infection** is invasion by harmful microbes (Bacteria, virus, fungi, parasite) into the body and their resultant ill-effects by toxins.

- **Inflammation** is a protective response by the body to variety of etiologic agents (infectious or non-infectious)

Inflammation

- It is a **body defense reaction** in order to eliminate or limit the spread of injurious agent, followed by removal of the necrosed cells and repair of damaged tissue

- **White blood cells or leukocytes**, are the body's major infection-fighting cells.

Causes

- **1. Infective agents** like bacteria, viruses and their toxins, fungi, parasites.
- **2. Physical agents** like heat, cold, radiation, mechanical trauma.
- **3. Chemical agents** like organic and inorganic poisons.
- **4. Immunological agents** like cell-mediated and antigenantibody reactions.
- **5. Inert materials** such as foreign bodies.

Types of inflammation

Acute inflammation

- **Rapid** in onset
- **Short lived**
- **Polymorphonuclear neutrophils** as inflammatory cells
- **Edema** is characteristic features

Chronic inflammation

- **Late** in onset
- **Longer** duration
- **Lymphocytes, macrophages, monocytes** as inflammatory cells
- **Granuloma formation** is characteristic feature

Classification

Acute

Rapid onset
Short duration
Odema
Neutrophills

Chronic

Late onset
Longer duration
Granuloma formation
Macrophage, lymphocyte

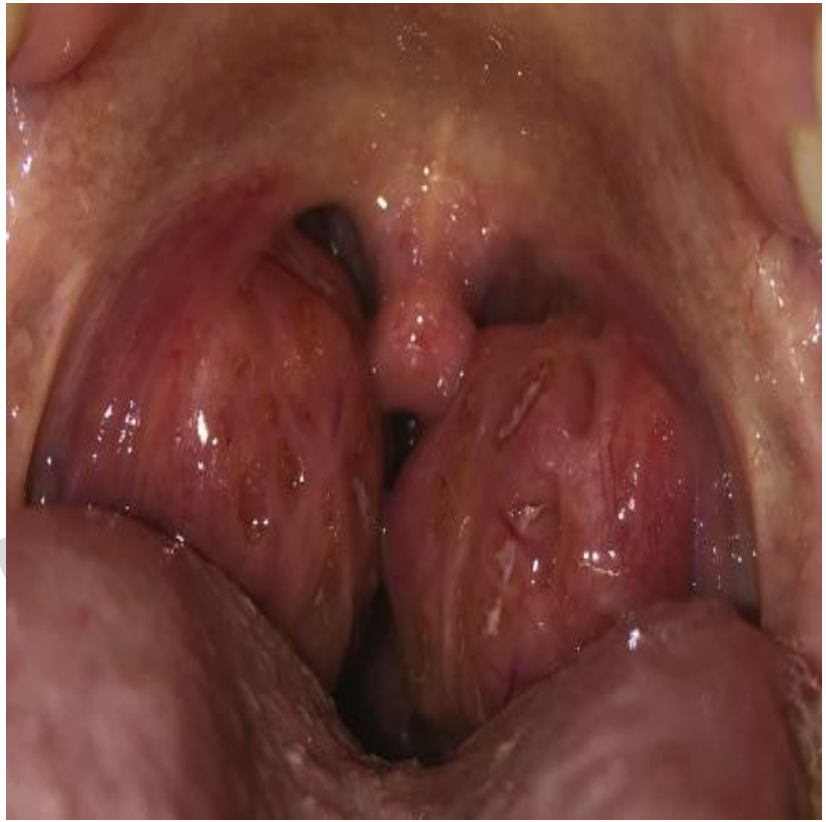
ACUTE INFLAMMATION

Dr. PRIYANKA SACHDEV, MD

CARDINAL SIGNS

Latin	English
Rubor	: redness
Calor	: ↑ed local temperature
Tumor	: swelling
Dolor	: pain
Functio laesa	: loss of function → Virchow

Celsus



POLLS 1

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Scan or Click to watch Haemodynamic Disorder

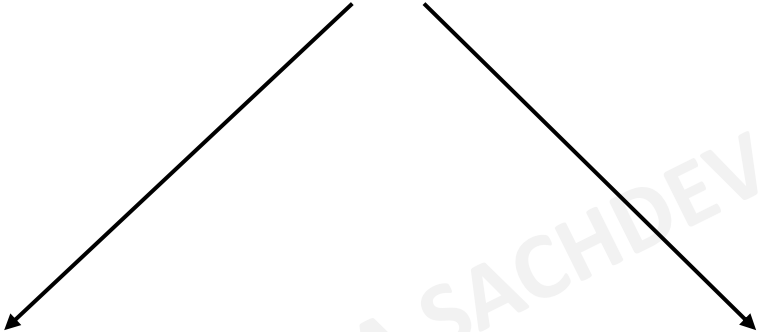
All are ‘celsus’ signs of inflammation except -

- a) Pain
- b) Swelling
- c) Cyanosis
- d) Redness

All are ‘celsus’ signs of inflammation except -

- a) Pain
- b) Swelling
- c) Cyanosis
- d) Redness

Acute inflammation



Vascular events

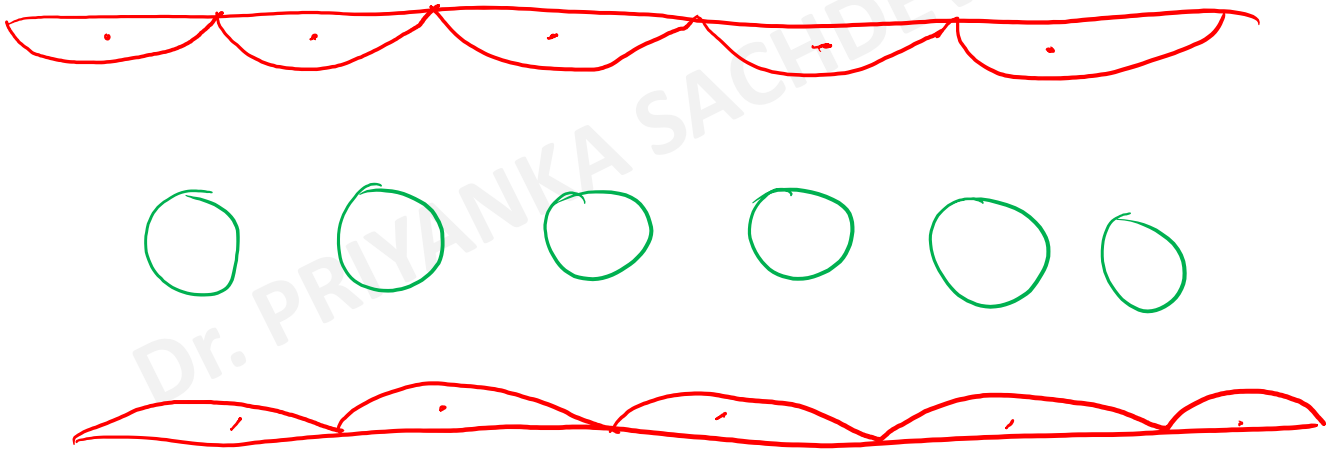
Cellular reaction

VASCULAR EVENTS

1. Transient vasoconstriction of arterioles
2. Persistent progressive vasodilatation
3. Elevate the local hydrostatic pressure
4. Increased vascular permeability
5. Slowing or stasis

CELLULAR EVENTS

1. Margination and pavementing
2. Rolling
3. Adhesion
4. Transmigration (diapedes)
5. Chemotaxis
6. Phagocytosis



VASCULAR EVENTS

1. Transient vasoconstriction of arterioles
2. Persistent progressive vasodilatation
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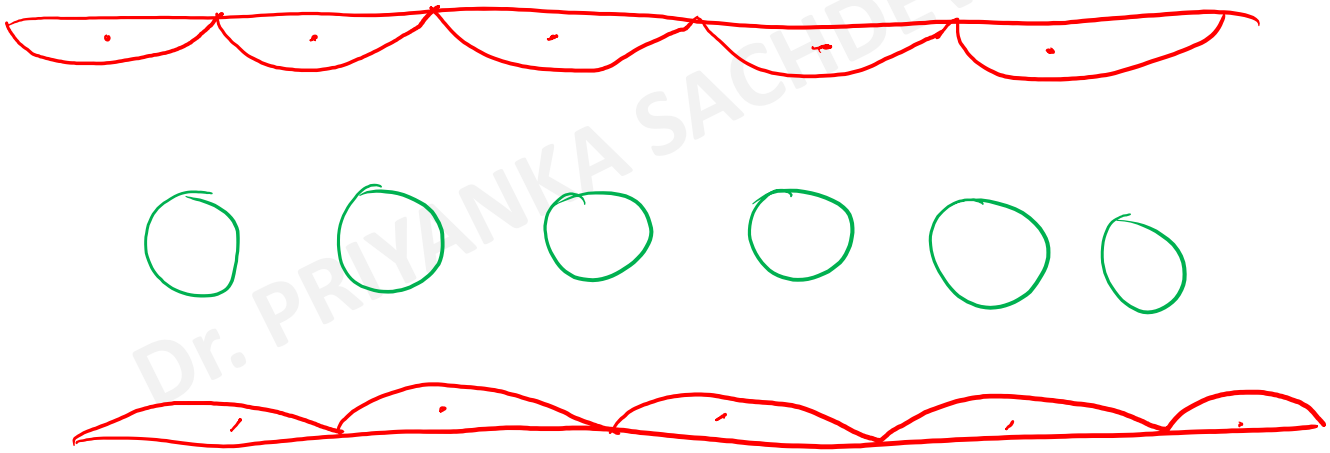
1.Transient vasoconstriction of arterioles

- Irrespective of the type of cell injury, immediate vascular response is of **transient vasoconstriction** of arterioles



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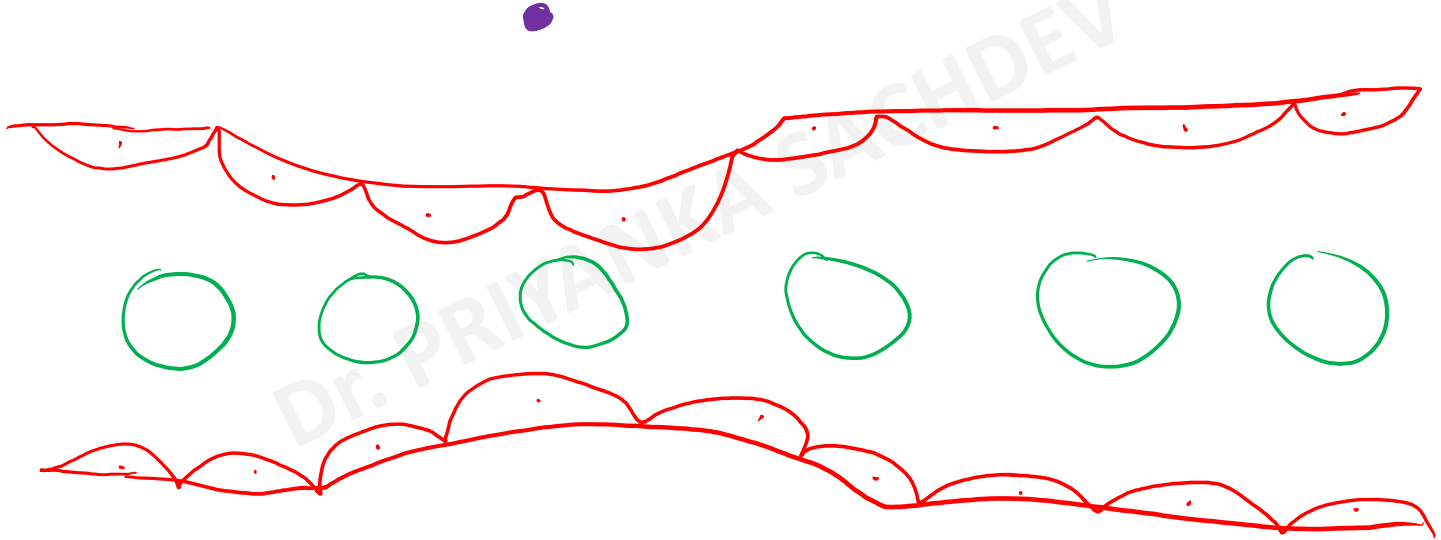

- Responsible for **blanching** seen immediately after injury.

- With mild injury→ **3-5 seconds**
- severe injury→ **5 minutes**

VASCULAR EVENTS

1. Transient vasoconstriction of arterioles
2. Persistent progressive vasodilatation
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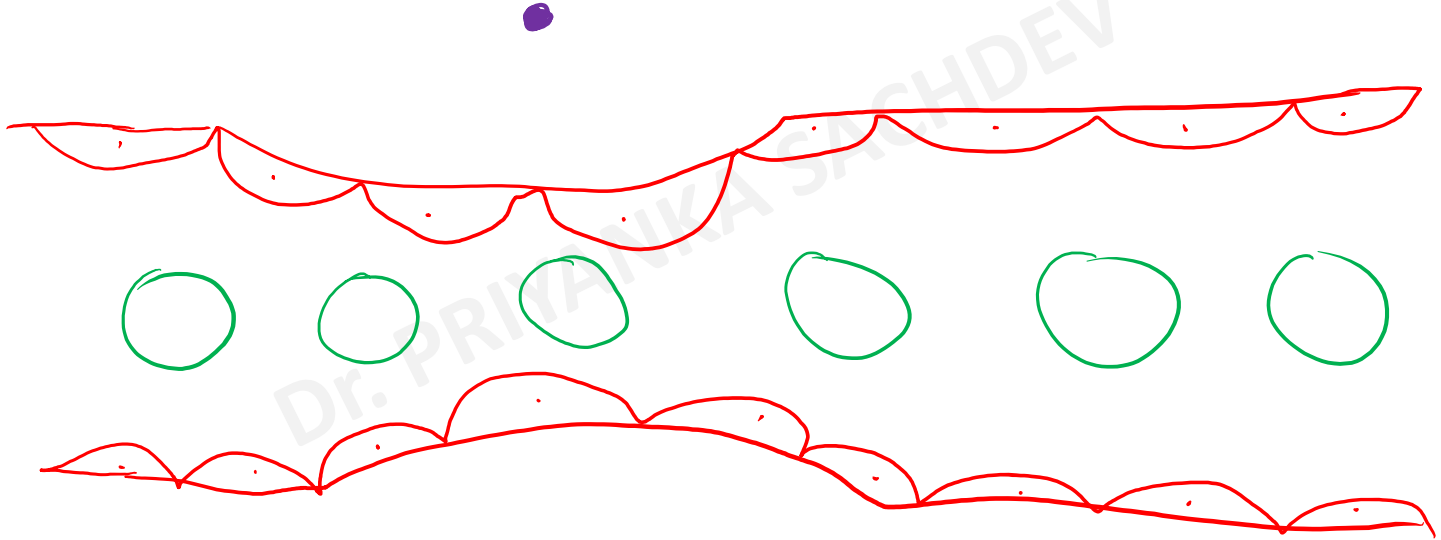
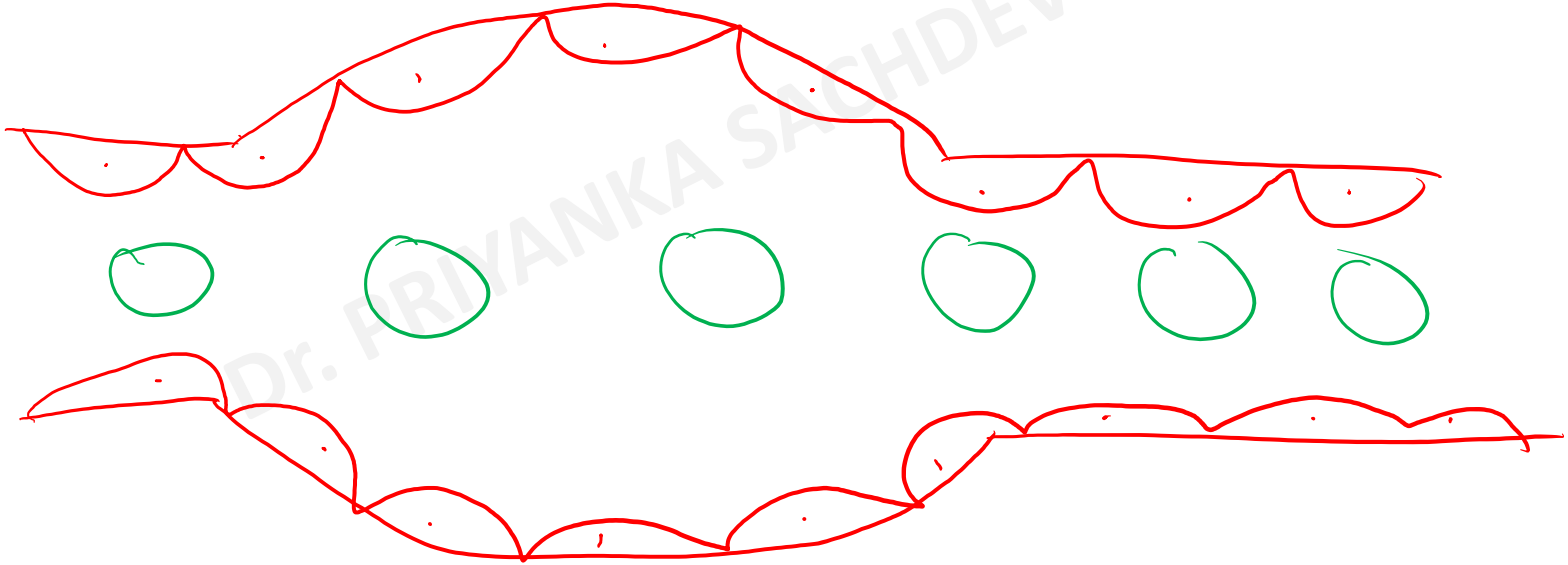
2. Persistent progressive vasodilatation

- Mainly arterioles, but also affect venules and capillaries.





- Vasodilatation results in increased blood volume→ **redness(rubor)** and **warmth (calor)** at the site of acute inflammation.

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VASCULAR EVENTS

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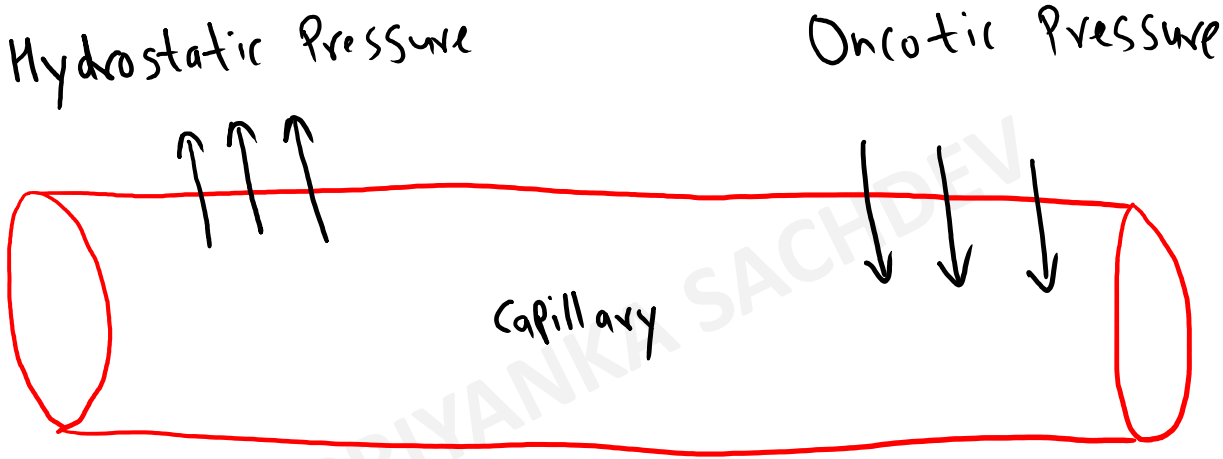
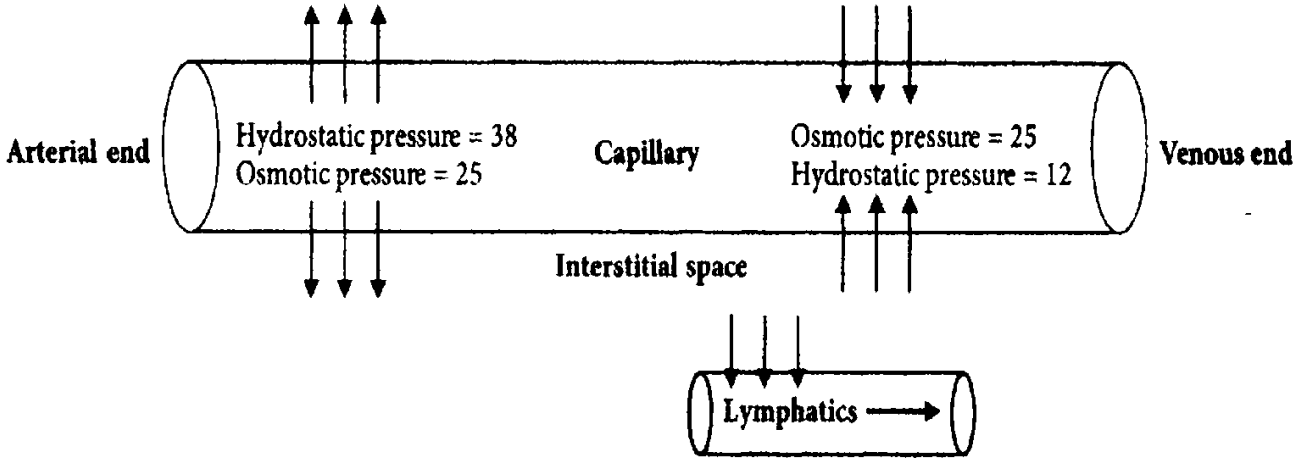
3. Elevate the local hydrostatic pressure



Starling's hypothesis



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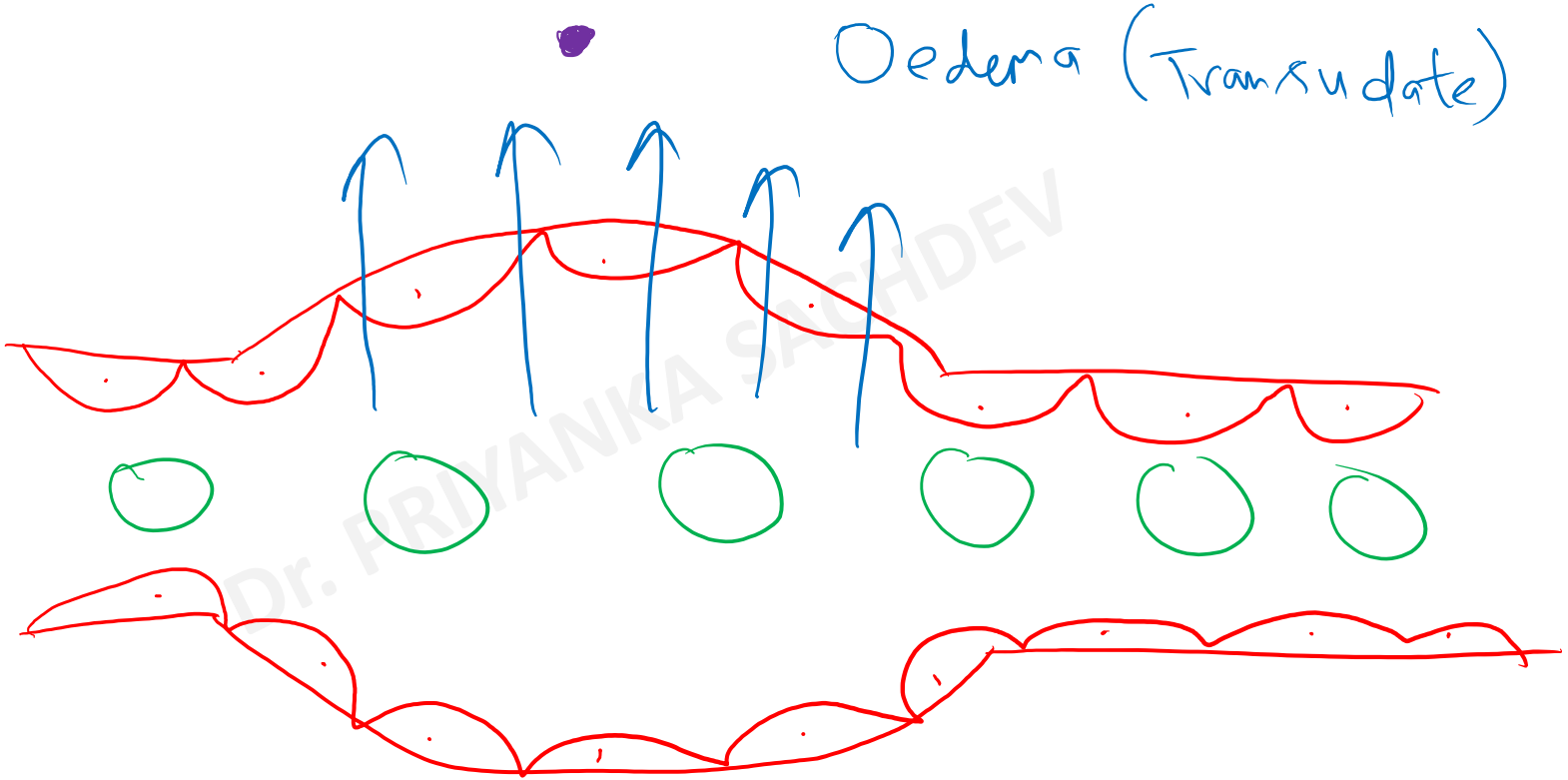
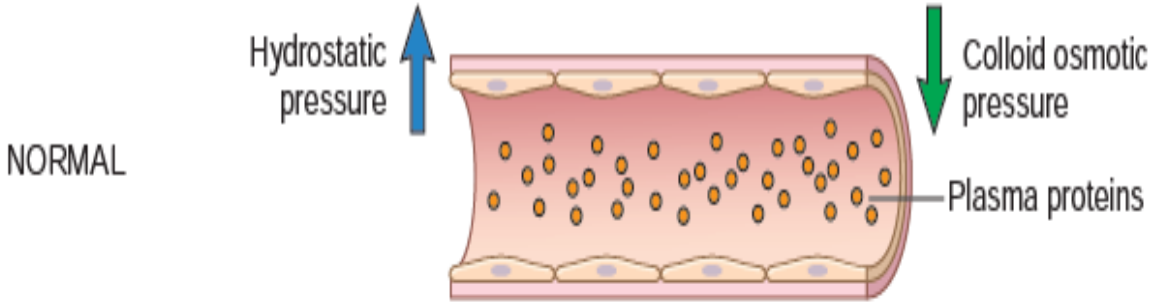
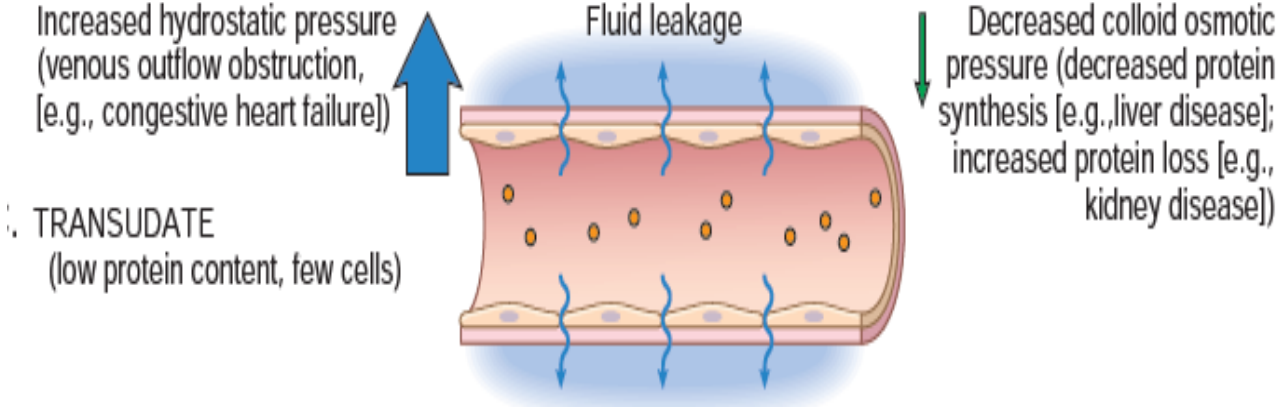



Hydrostatic pressure
Colloid osmotic pressure
NORMAL
Plasma proteins


Increased hydrostatic pressure (venous outflow obstruction, [e.g., congestive heart failure])
Fluid leakage
Decreased colloid osmotic pressure (decreased protein synthesis [e.g.,liver disease]; increased protein loss [e.g., kidney disease])
TRANSUDATE
(low protein content, few cells)

- Transudation of fluid into the extracellular space → Oedema→ **Transudate**

- Swelling at the local site of acute inflammation **(tumor)**

VASCULAR EVENTS

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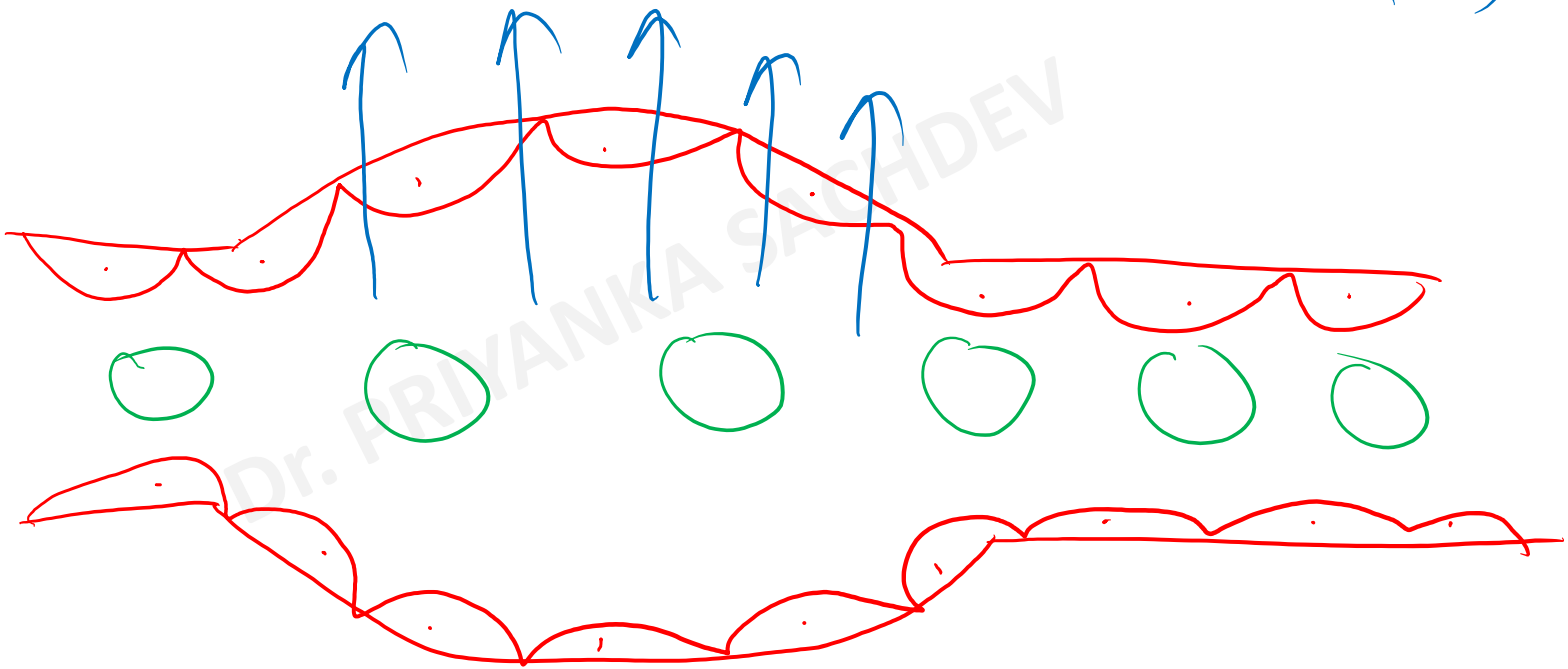
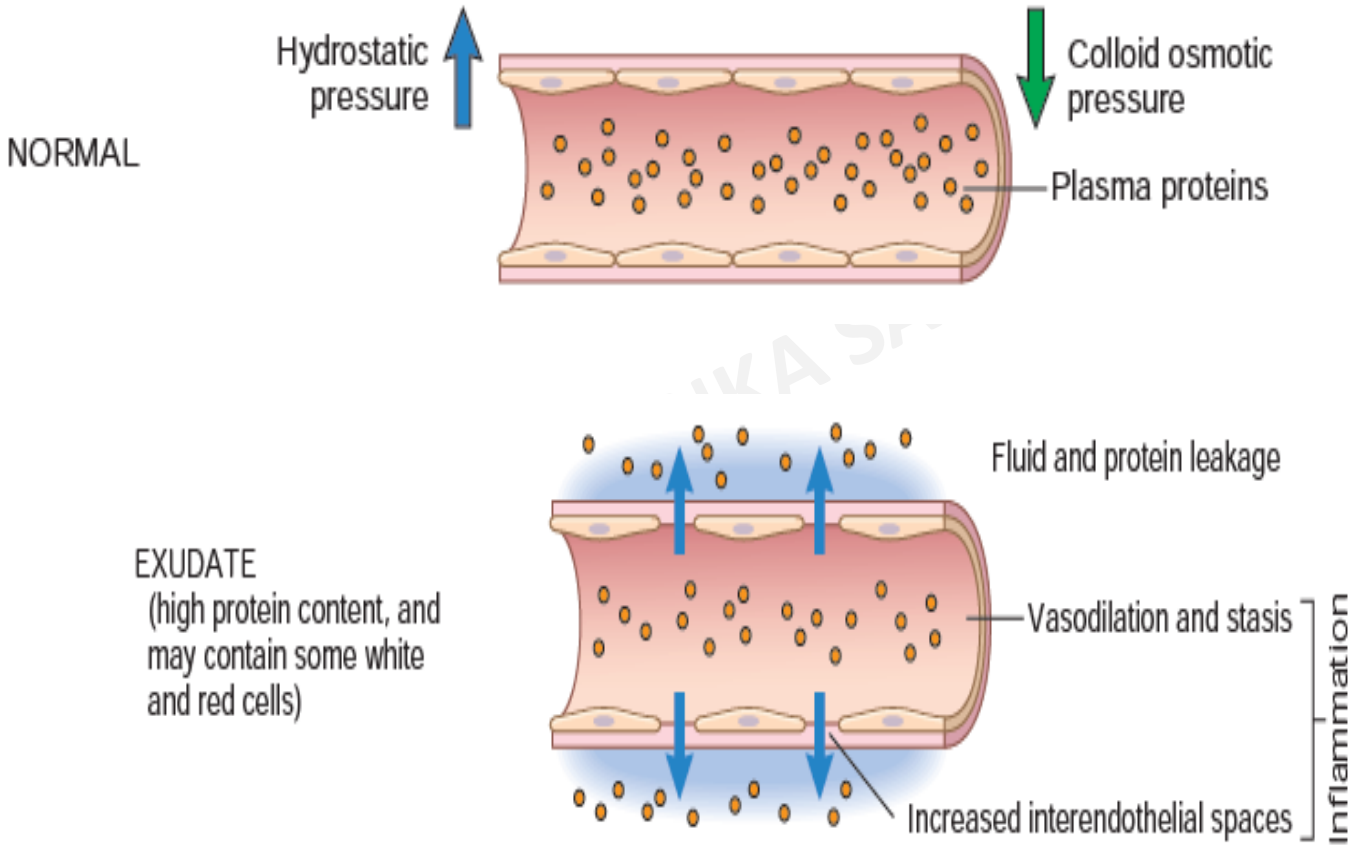
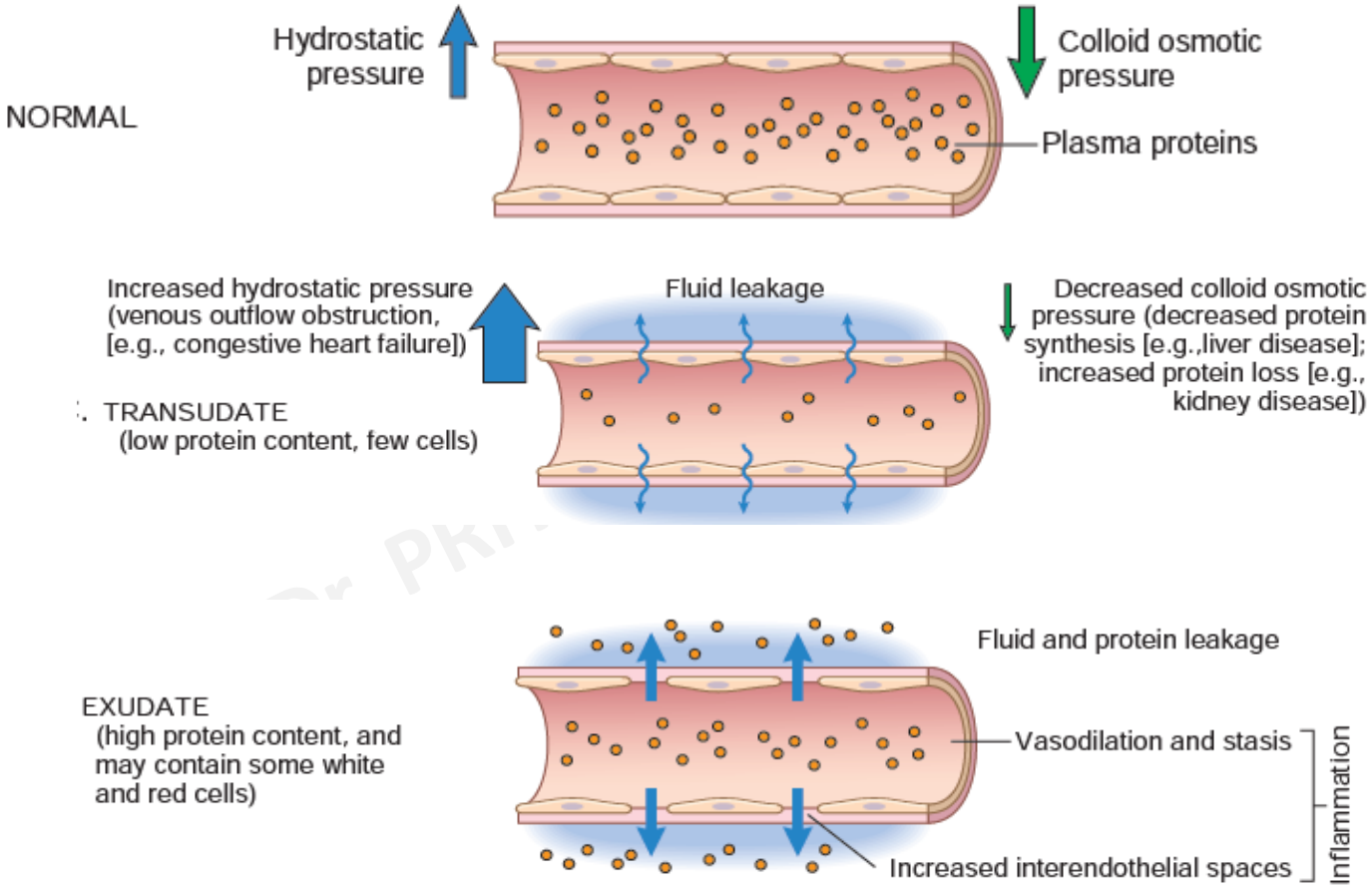
4. Increased vascular permeability

- Increased vascular permeability is the **hallmark of acute inflammation**

Oedema (Transudate)




NORMAL
Hydrostatic pressure
Colloid osmotic pressure
Plasma proteins
EXUDATE
(high protein content, and may contain some white and red cells)
Fluid and protein leakage
Vasodilation and stasis
Increased interendothelial spaces
Inflammation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EXUDATE
(high protein content, and may contain some white and red cells)
Fluid and protein leakage
Vasodilation and stasis
Increased interendothelial spaces
Inflammation

- This leads to escape of protein rich fluid (**Oedema → Exudate**) and leukocytes in extravascular space.
- Most affected vessels are **venules**

- It is responsible for **swelling (tumor)** seen in acute inflammation.

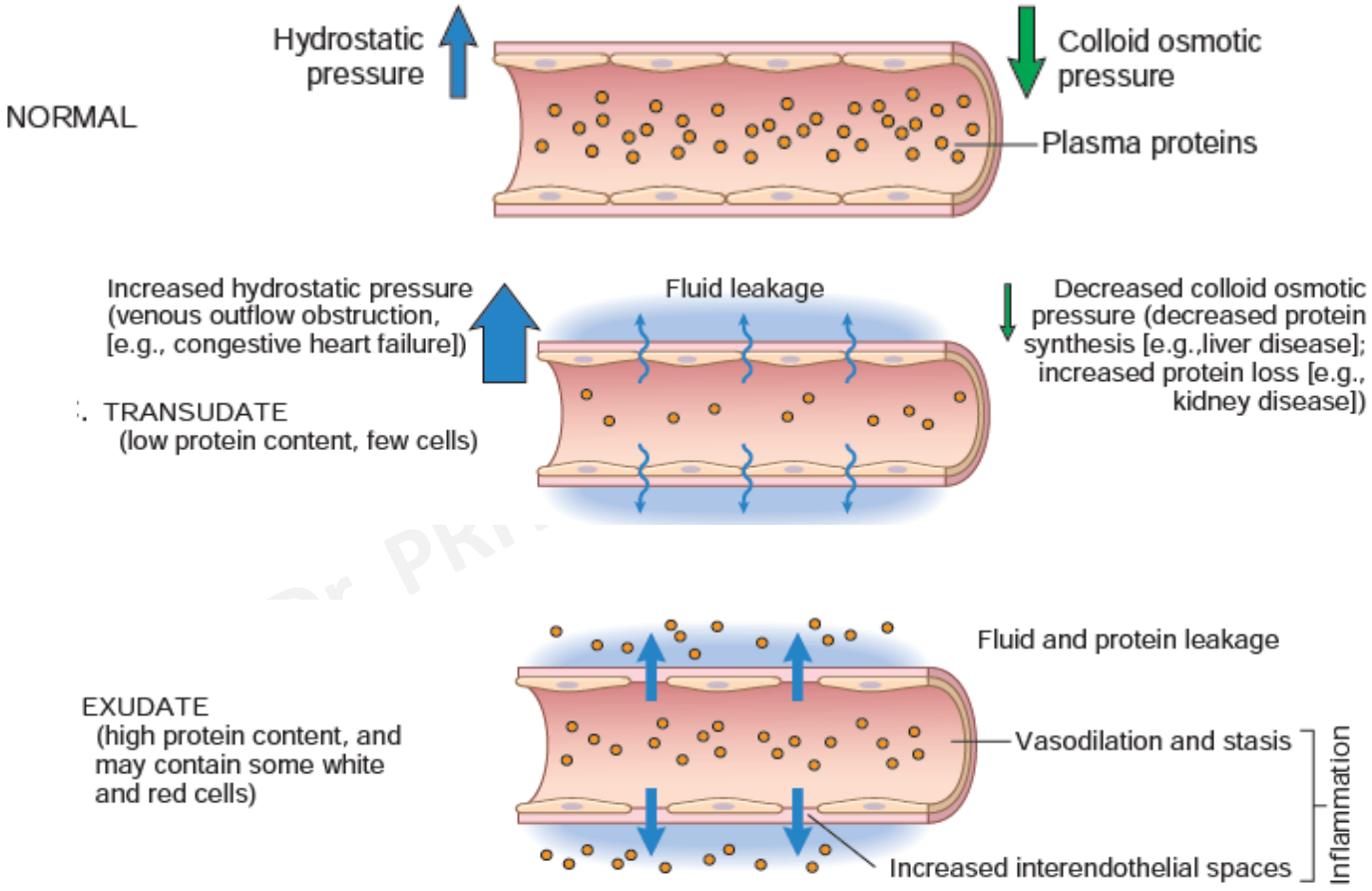
- Leucocytes stick to the vascular endothelium and then move and migrate through the gaps between the endothelial cells into the extravascular space.

- This process is known as **transmigration.**

REMEMBER

- **In the initial stage**, the escape of fluid is due to **Elevation in hydrostatic pressure.**
- This is **transudate** in nature.

- **But subsequently**, the escape of fluid is due **increased vascular permeability of Microvasculature**
- This is **exudate** in nature.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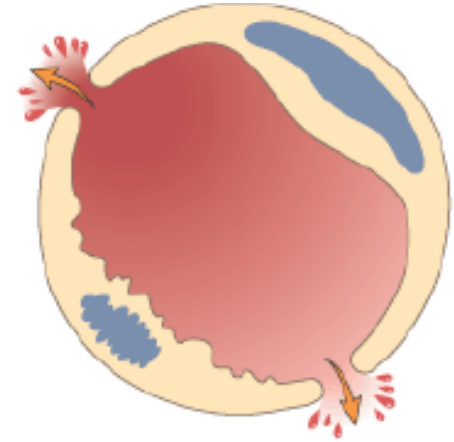
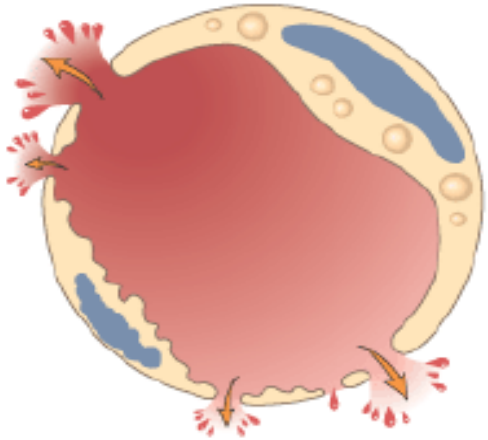
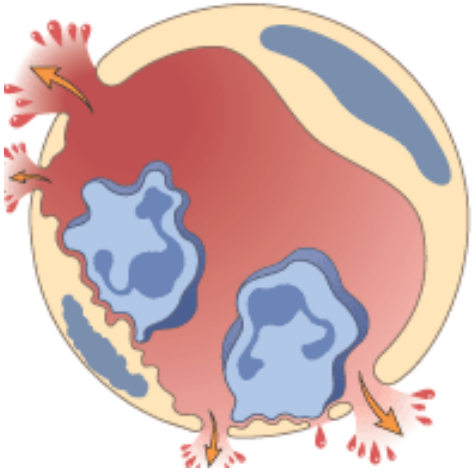
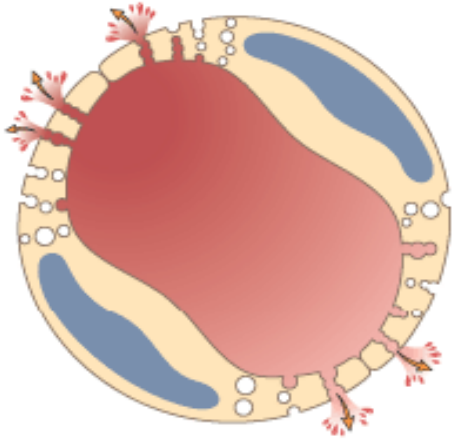
Altered Vascular Permeability mechanisms

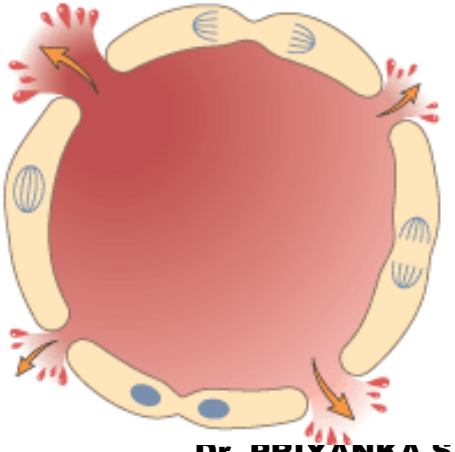
1. Formation of endothelial gaps
2. Direct endothelial injury
3. Leukocyte mediated endothelial cell injury
4. Increased transcytosis
5. Leakage from new blood vessels











Altered Vascular Permeability mechanisms

1. Formation of endothelial gaps
2. Direct endothelial injury
3. Leukocyte mediated endothelial cell injury
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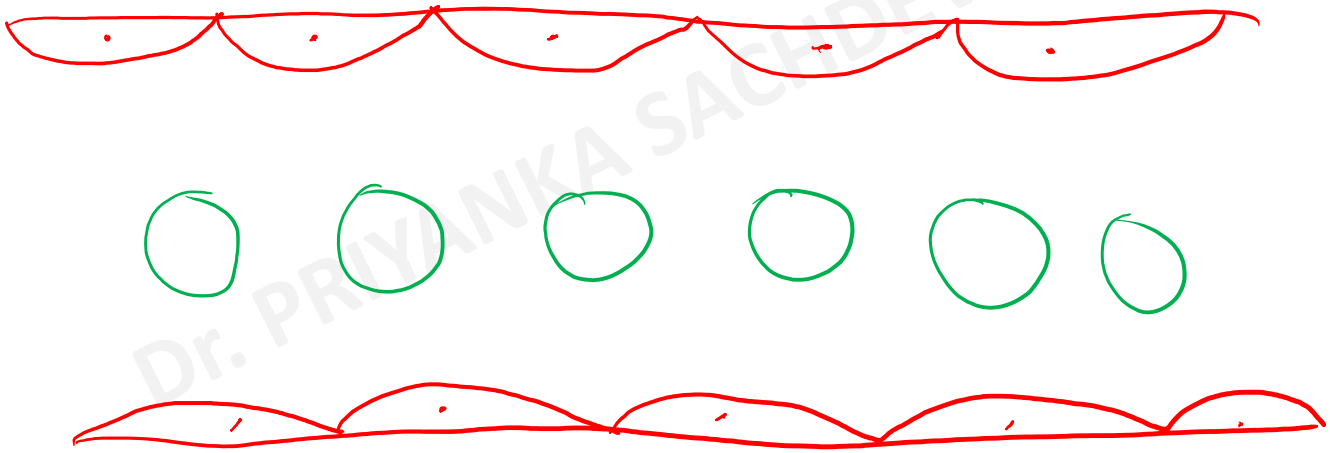
Formation of endothelial gaps

- **Immediate transient response**

- It is the **most common mechanism** for increased permeability.
- It occurs due to **contraction of endothelial cell cytoskeleton**



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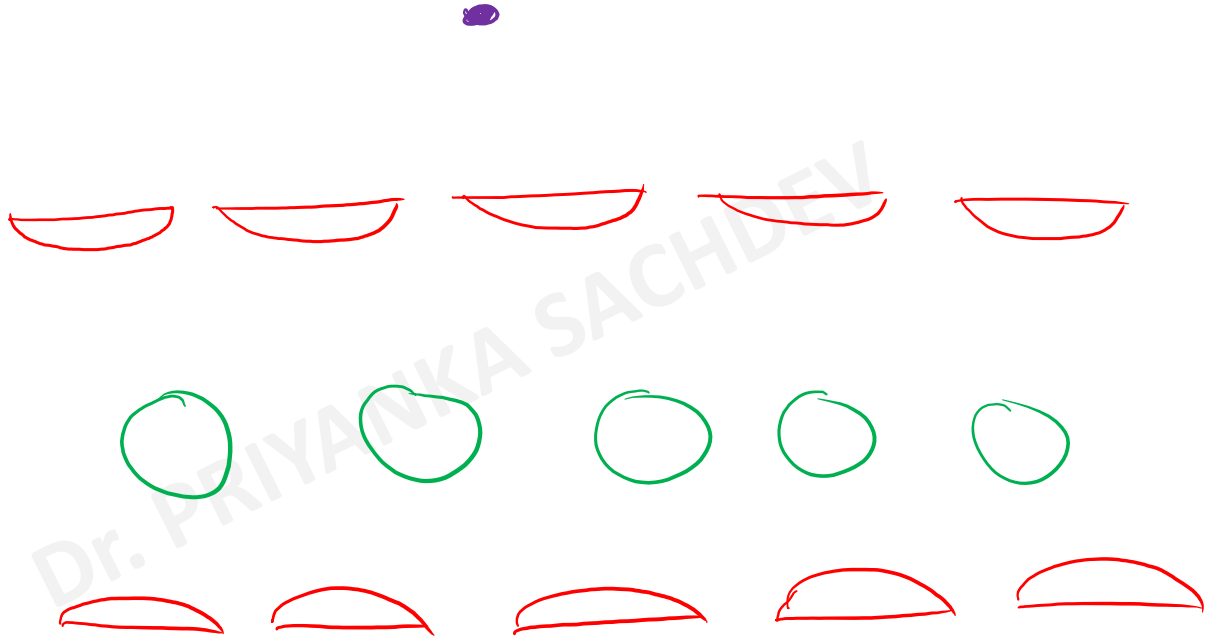
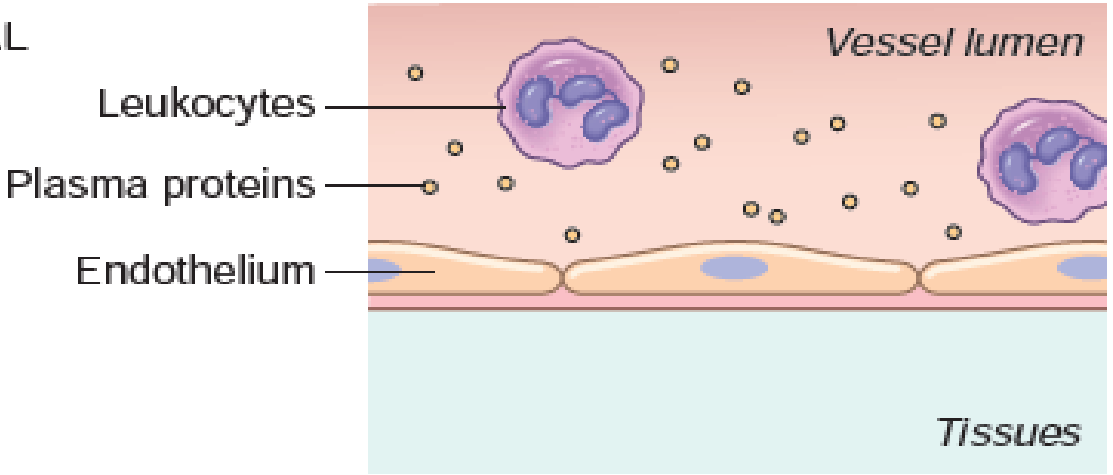
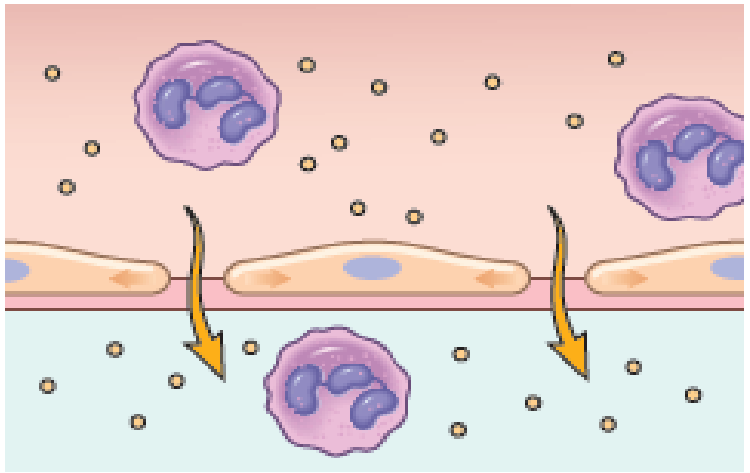


A. NORMAL



B. RETRACTION OF ENDOTHELIAL CELLS

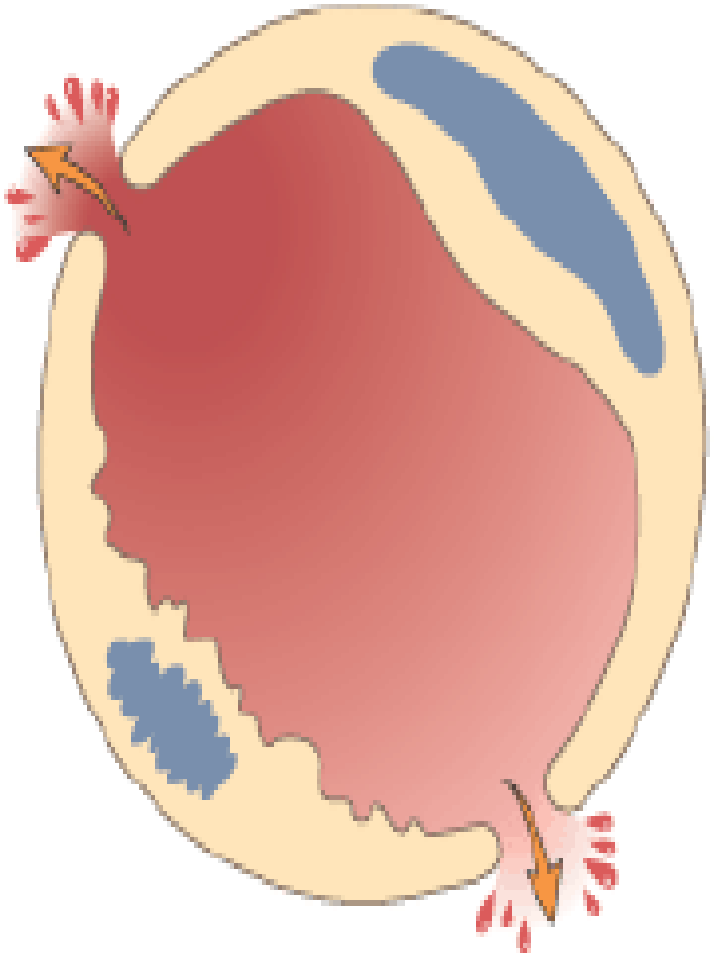
- Induced by histamine, other mediators
- Rapid and short-lived (minutes)



ACHDEV

Gaps due to endothelial contraction

- Venules
- Vasoactive mediators (histamine, leukotrienes, etc.)
- Most common
- Fast and short-lived (minutes)



- Important mediators involved are **histamine** , bradykinin, leukotrienes and later cytokines (IL-1, TNF, IFN - y) are also involved.

- The most commonly affected vessels are **venules**

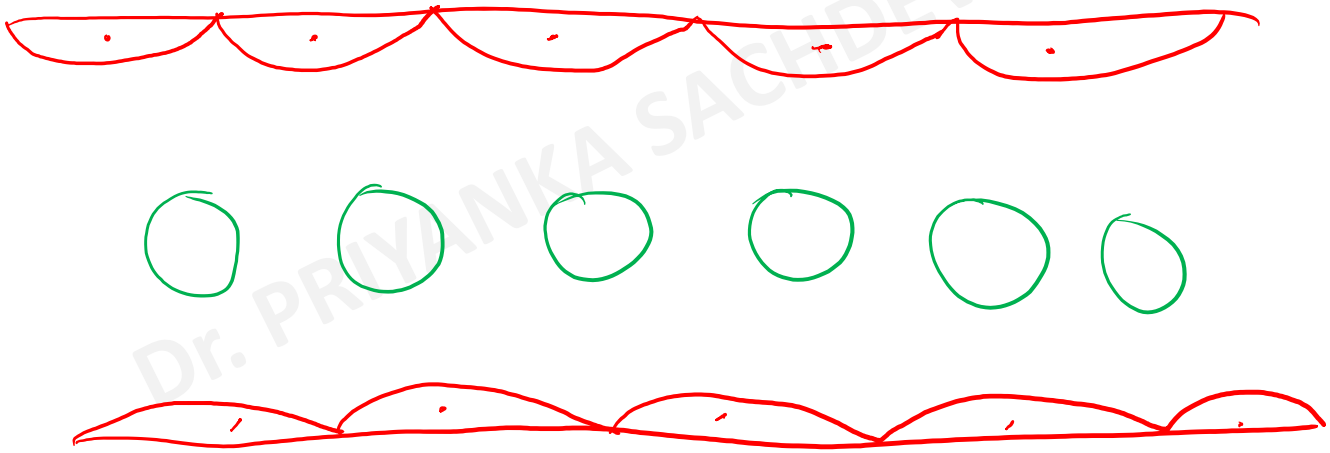
- The response is **rapid, reversible and short lived.**

Altered Vascular Permeability mechanisms

1. Formation of endothelial gaps
2. Direct endothelial injury
3. Leukocyte mediated endothelial cell injury
4. Increased transcytosis
5. Leakage from new blood vessels

Direct endothelial injury

- **Immediate sustained (prolonged) response**
- This response is **rapid but long lived.**
- It occurs due to **direct injury causing necrosis and detachment of endothelial cells by toxins, infections or burns**
- **All levels of microcirculation** are affected including venules, capillaries and arterioles



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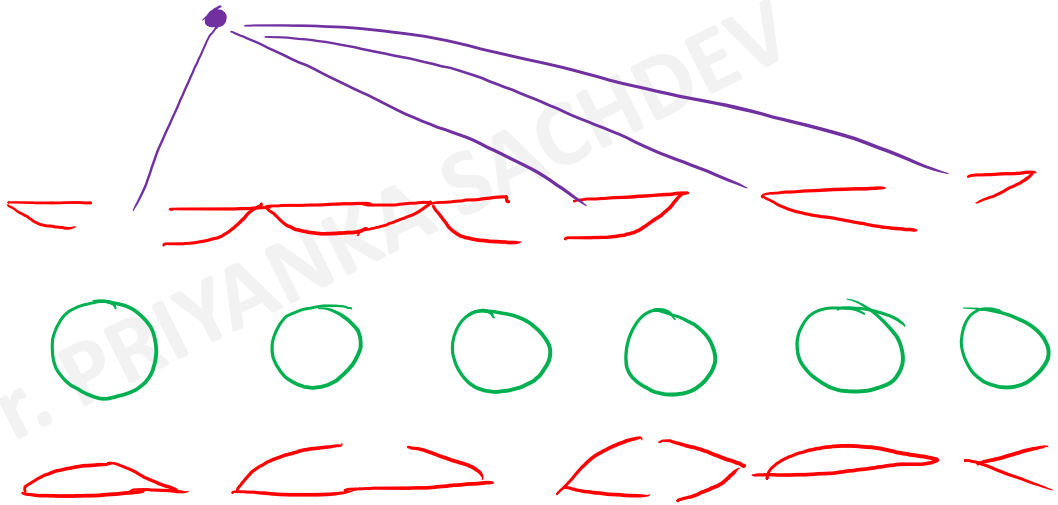
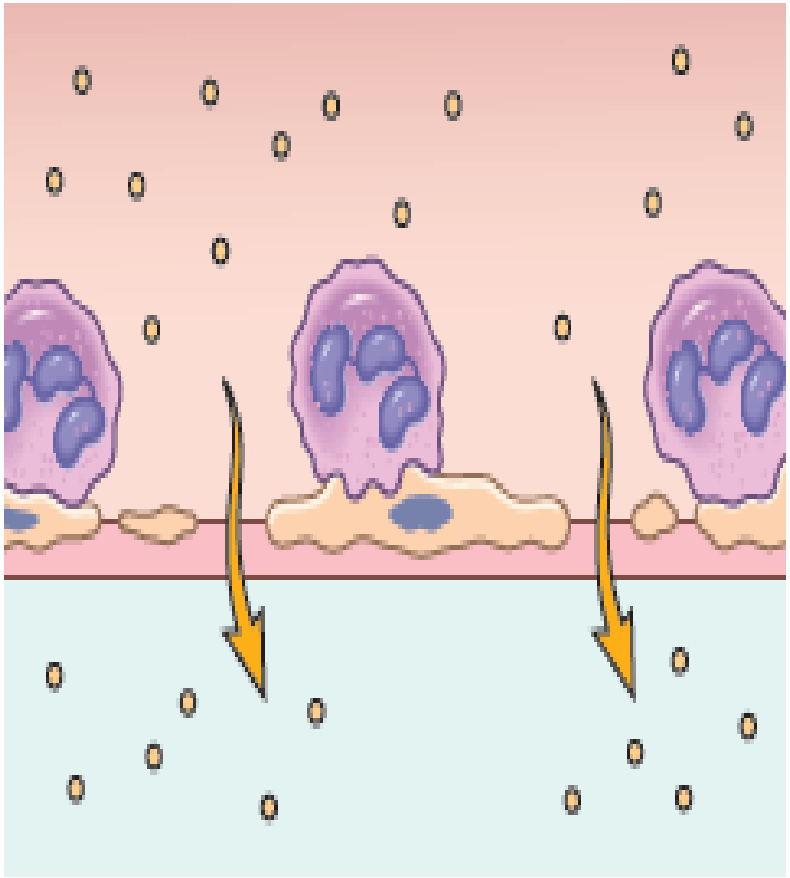


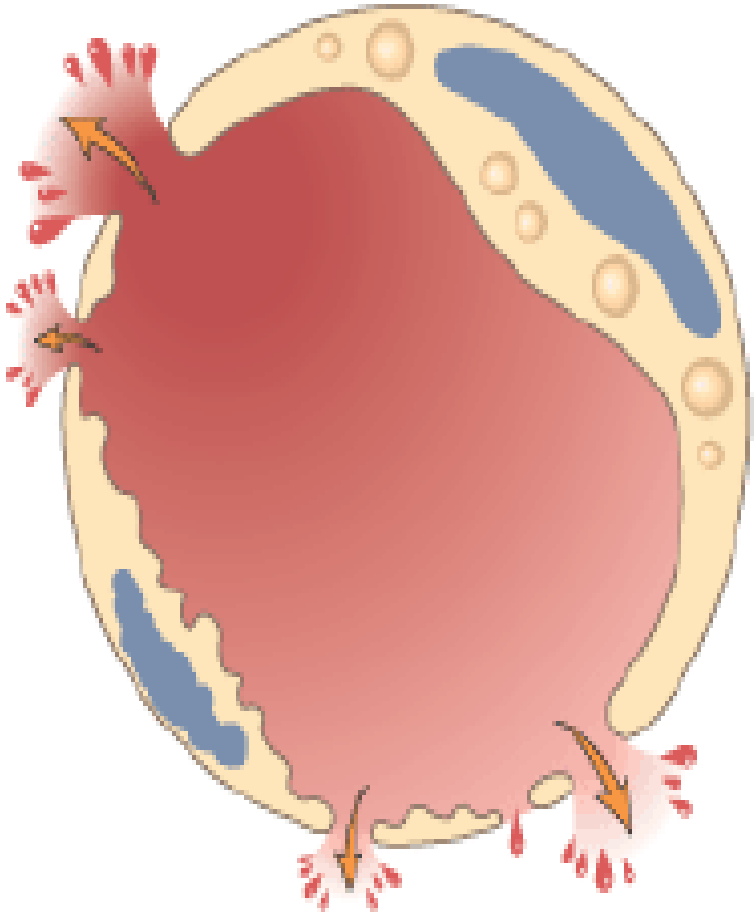
ENDOTHELIAL INJURY

- Caused by burns, some microbial toxins
- Rapid; may be long-lived (hours to days)



Direct injury

- Arterioles, capillaries, and venules
- Toxins, burns, chemicals
- Fast and may be long-lived (hours to days)



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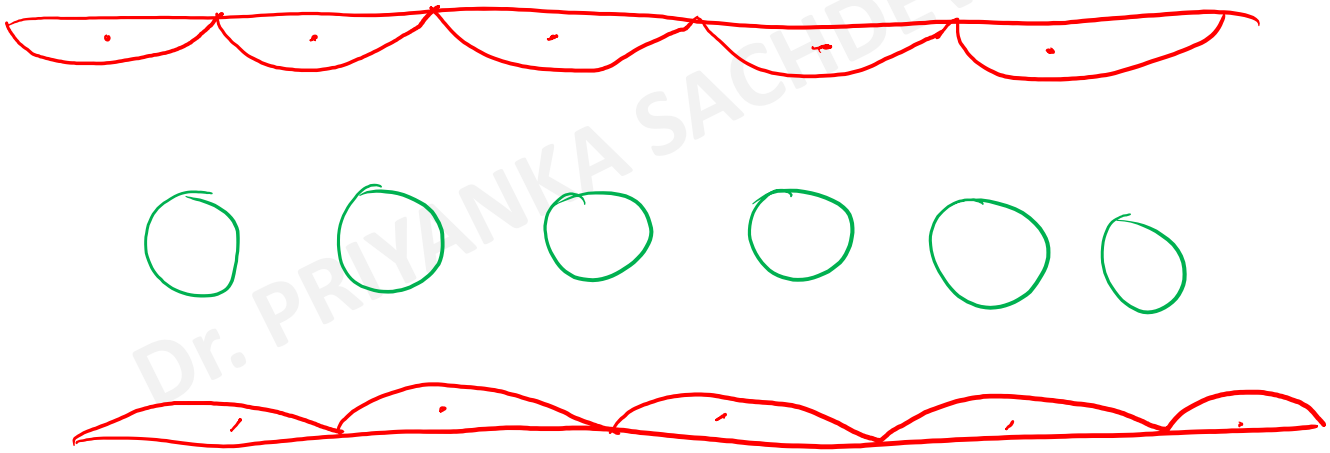
Leukocyte mediated endothelial cell injury

Delayed prolonged (sustained) response

- **Leukocytes** are activated and cause endothelial cell injury.
- It affects **venules (mostly); and pulmonary and glomerular capillaries**



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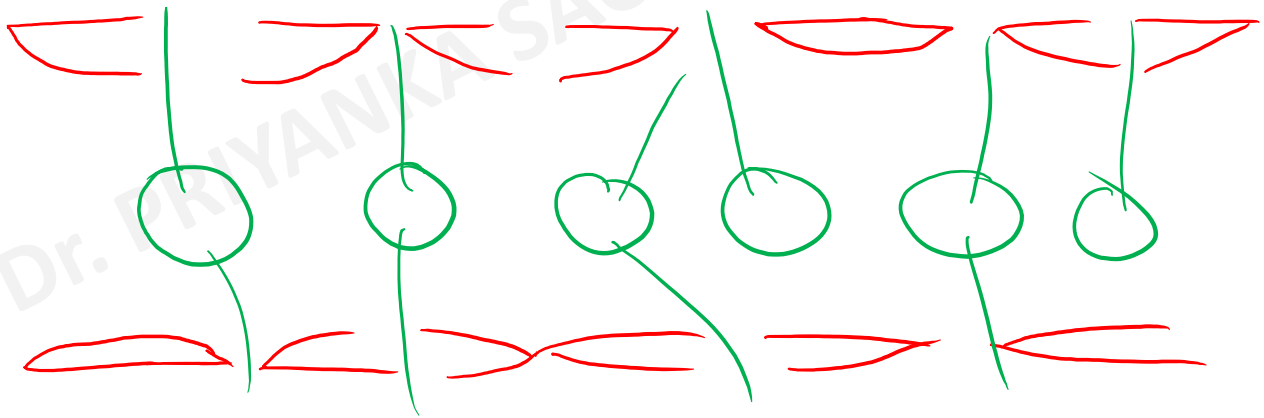
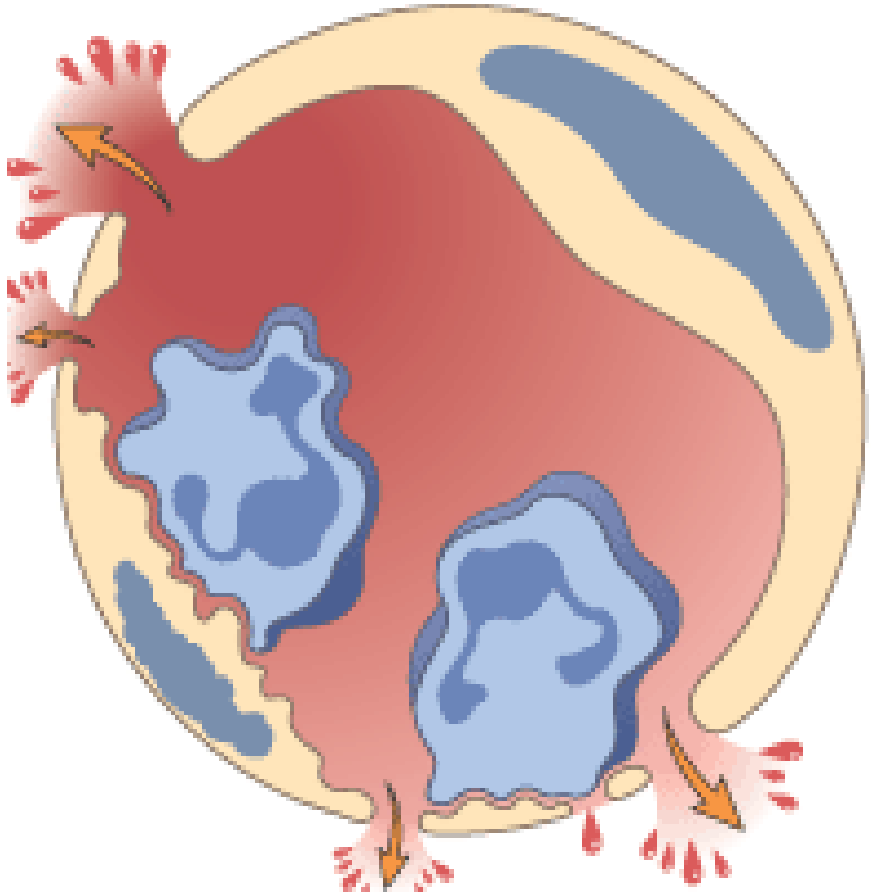


Leukocyte-dependent injury

- Mostly venules
- Pulmonary capillaries
- Late response
- Long-lived (hours)

- Long-lived (hours)



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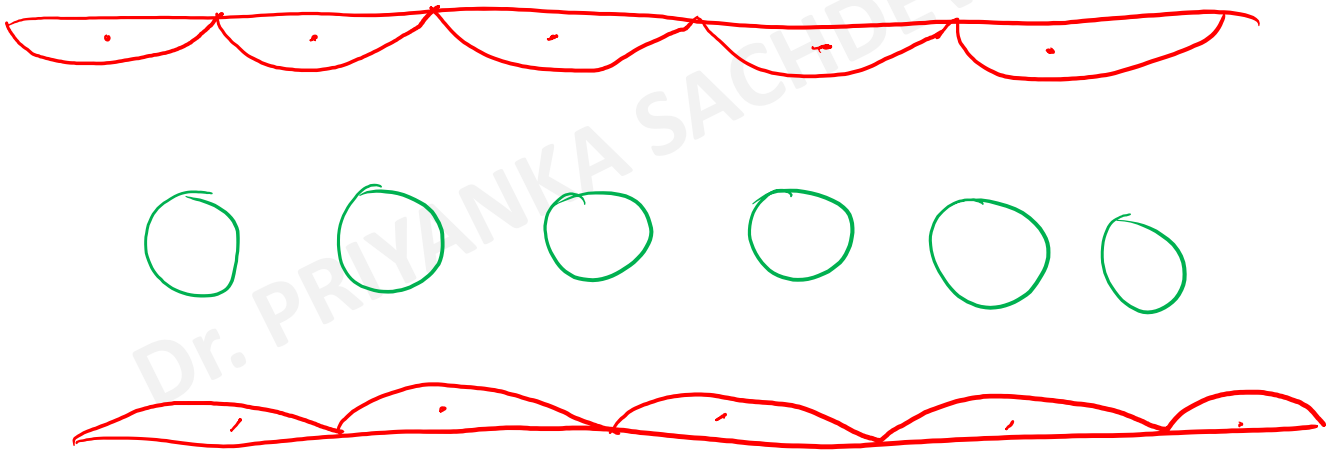
Increased transcytosis

- It affects **venules**
- It is caused by formation of **vesiculo-vacuolar organelles** near intercellular junction by **histamine and VEGF**



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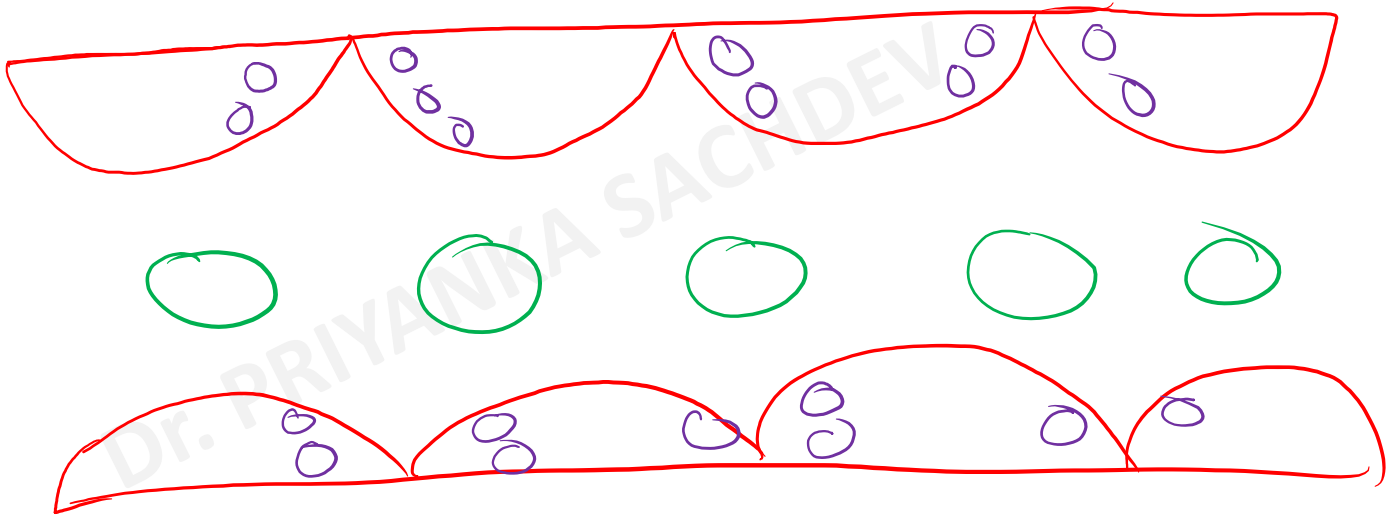
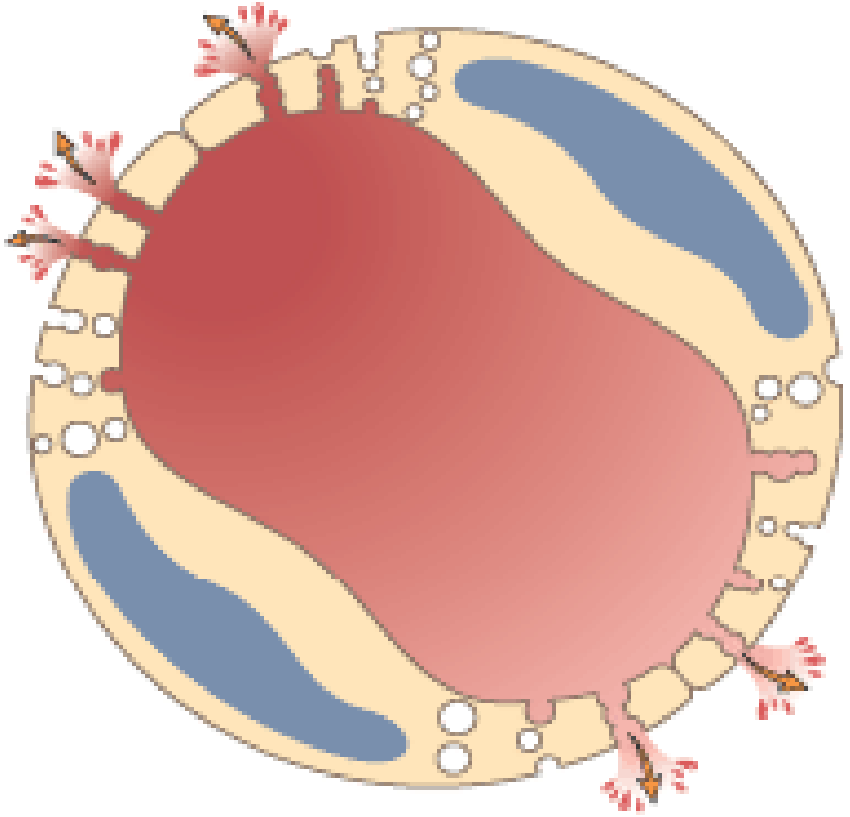


Increased transcytosis

- Venules
- Vascular endothelium–de
  growth factor



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Altered Vascular Permeability mechanisms

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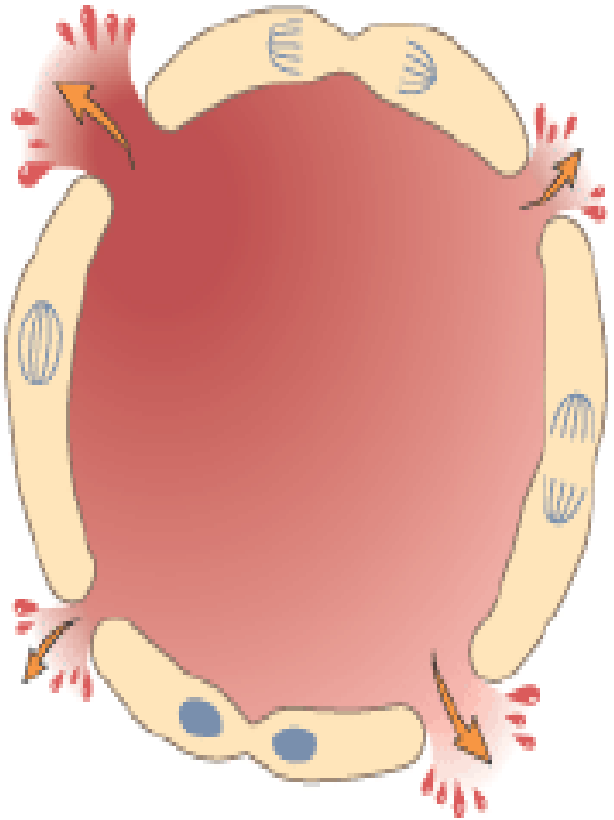
Leakage from new blood vessels

- It occurs at the site of **angiogenesis** as new blood vessels are leaky
- **VEGF**

New blood vessel formation

- Sites of angiogenesis
- Persists until intercellular junctions form



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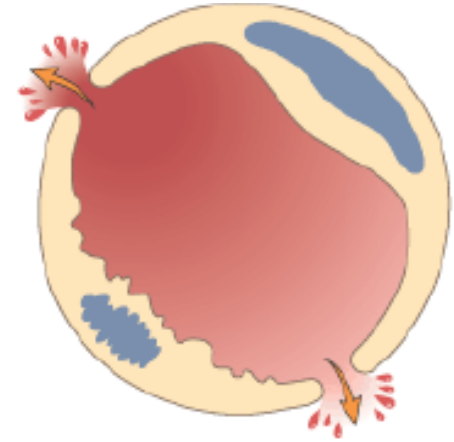
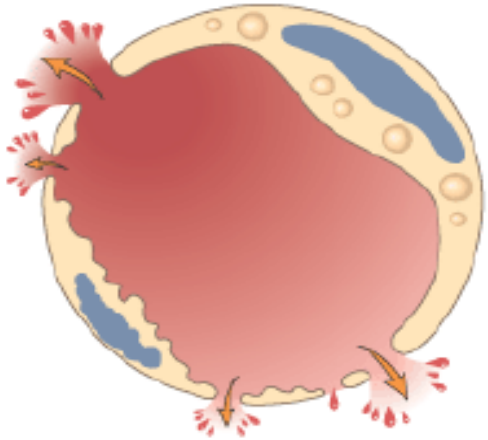
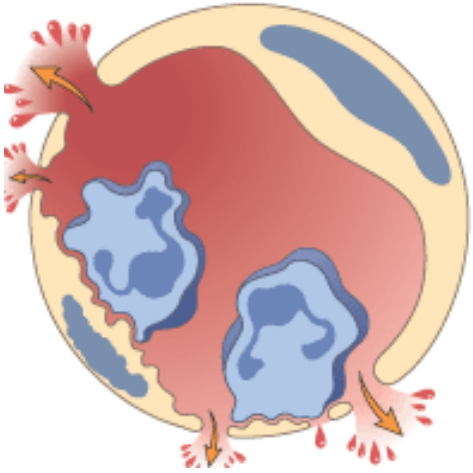
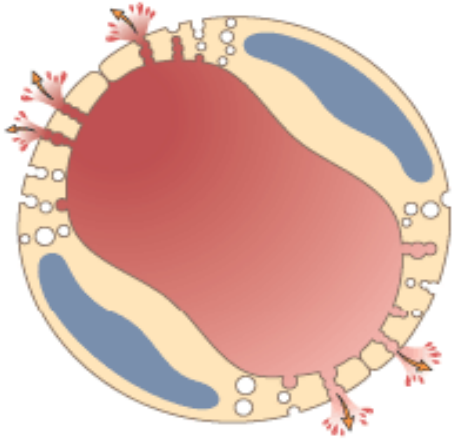
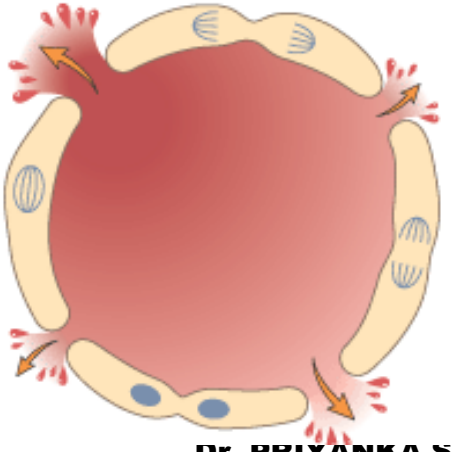
4. Increased transcytosis
5. Leakage from new blood vessels

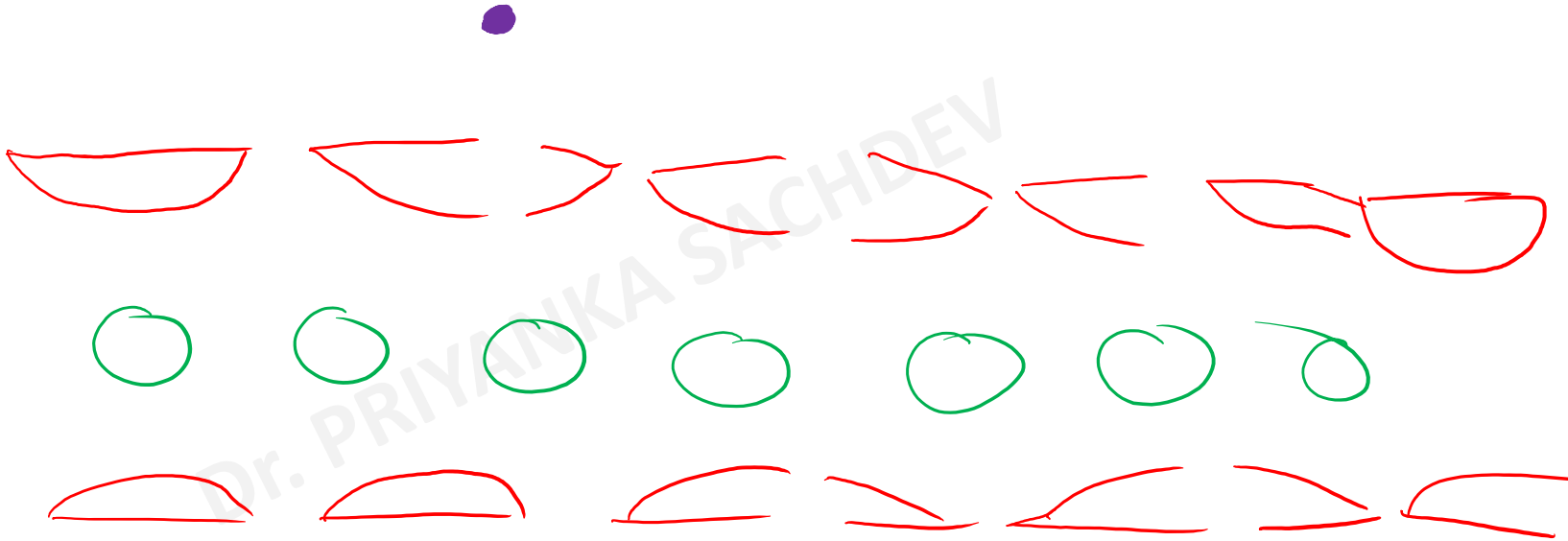












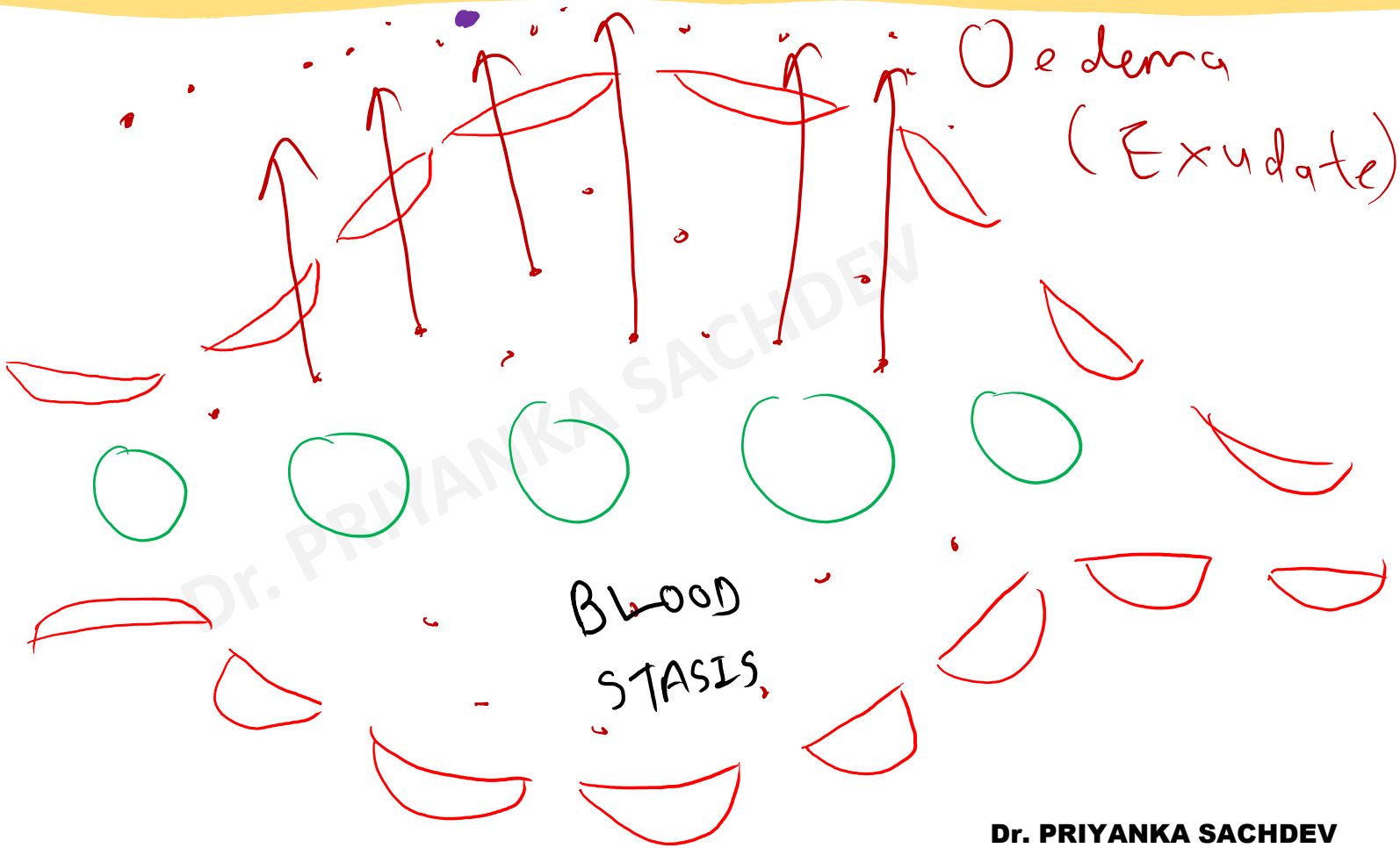
MECHANISM	MICROVASCULATURE	RESPONSE TYPE	PATHOGENESIS	EXAMPLES
1. *Endothelial cell contraction*	Venules	Immediate transient (15-30 min)	Histamine, bradykinin, others	Mild thermal injury
2. *Direct endothelial cell injury*	Arterioles, venules, capillaries	Immediate prolonged (hrs to days), or delayed (2-12 hrs) prolonged (hrs to days)	Cell necrosis and detachment	Moderate to severe burns, severe bacterial infection, radiation injury
3. *Leucocyte-mediated endothelial injury*	Venules, capillaries	Delayed, prolonged	Leucocyte activation	Pulmonary venules and capillaries
5. *Neovascularisation*	All levels	Any type	Angiogenesis, VEGF	Healing, tumours

VASCULAR EVENTS

1. Transient vasoconstriction of arterioles
2. Persistent progressive vasodilatation
3. Elevate the local hydrostatic pressure
4. Increased vascular permeability
5. Slowing or stasis

5. Slowing or stasis

- Increased concentration of red cells → **raised blood viscosity**



REVISION OF VASCULAR EVENTS

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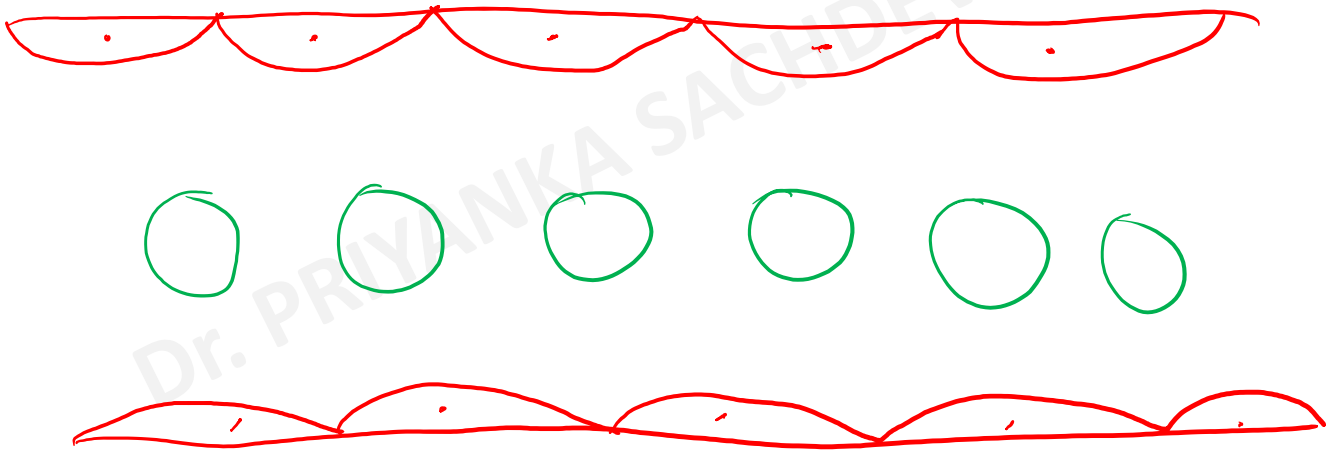

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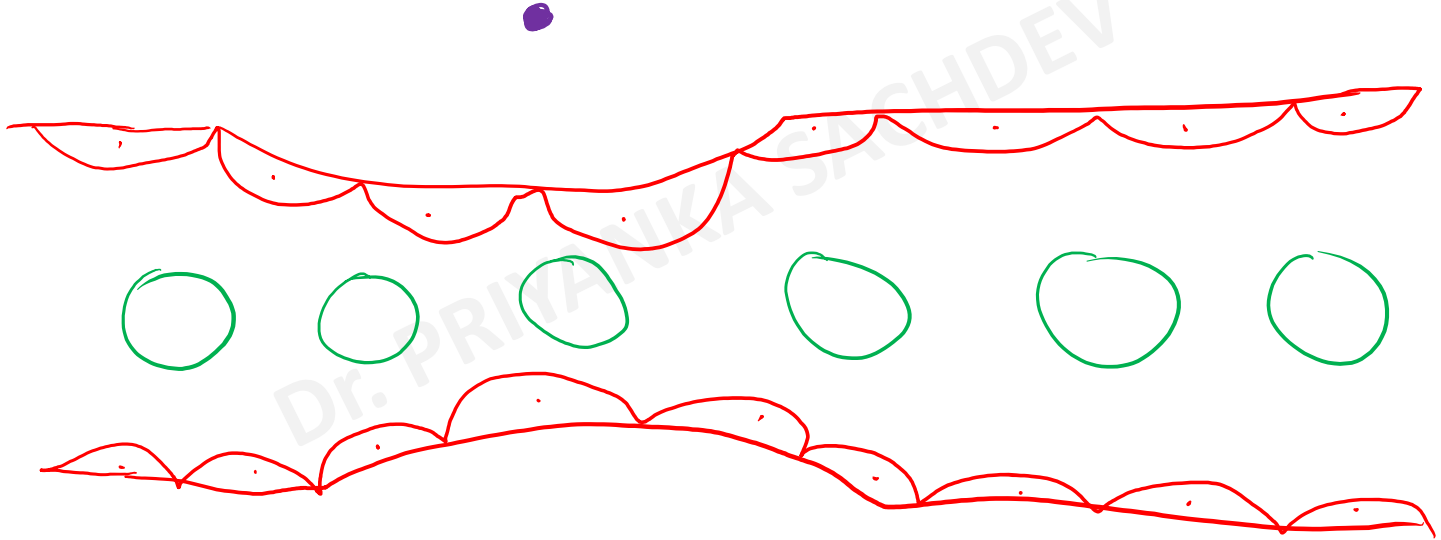
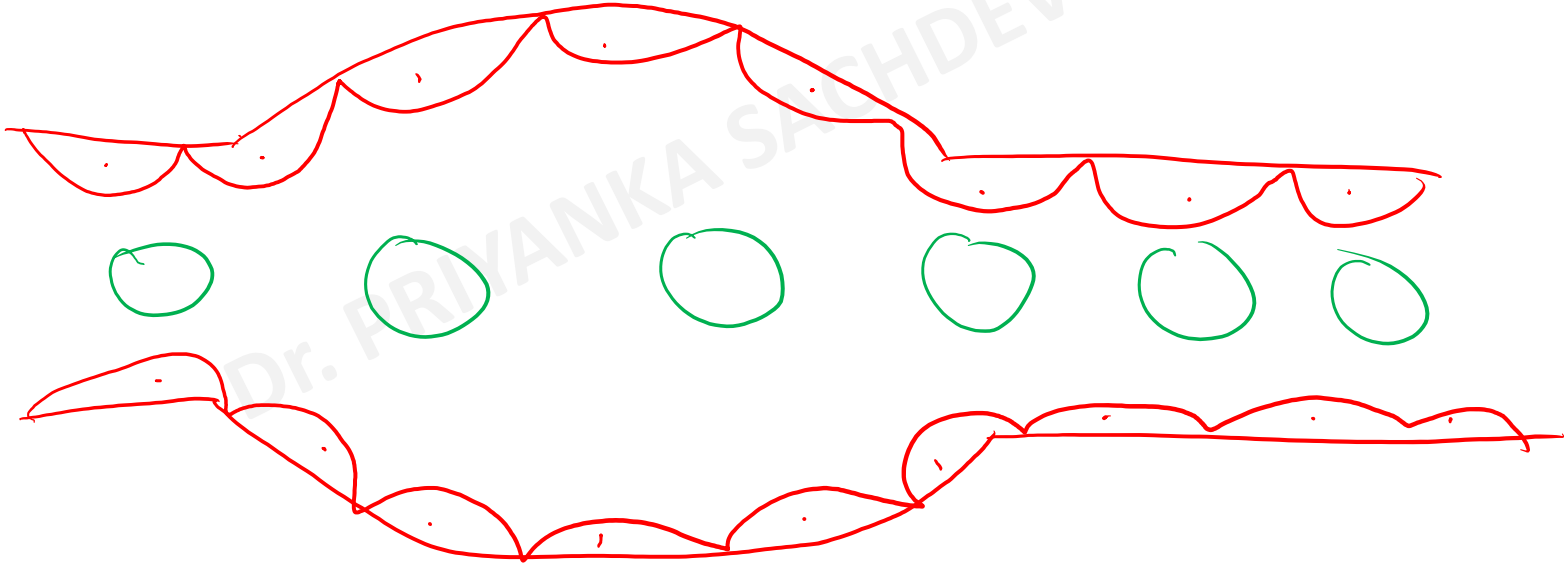
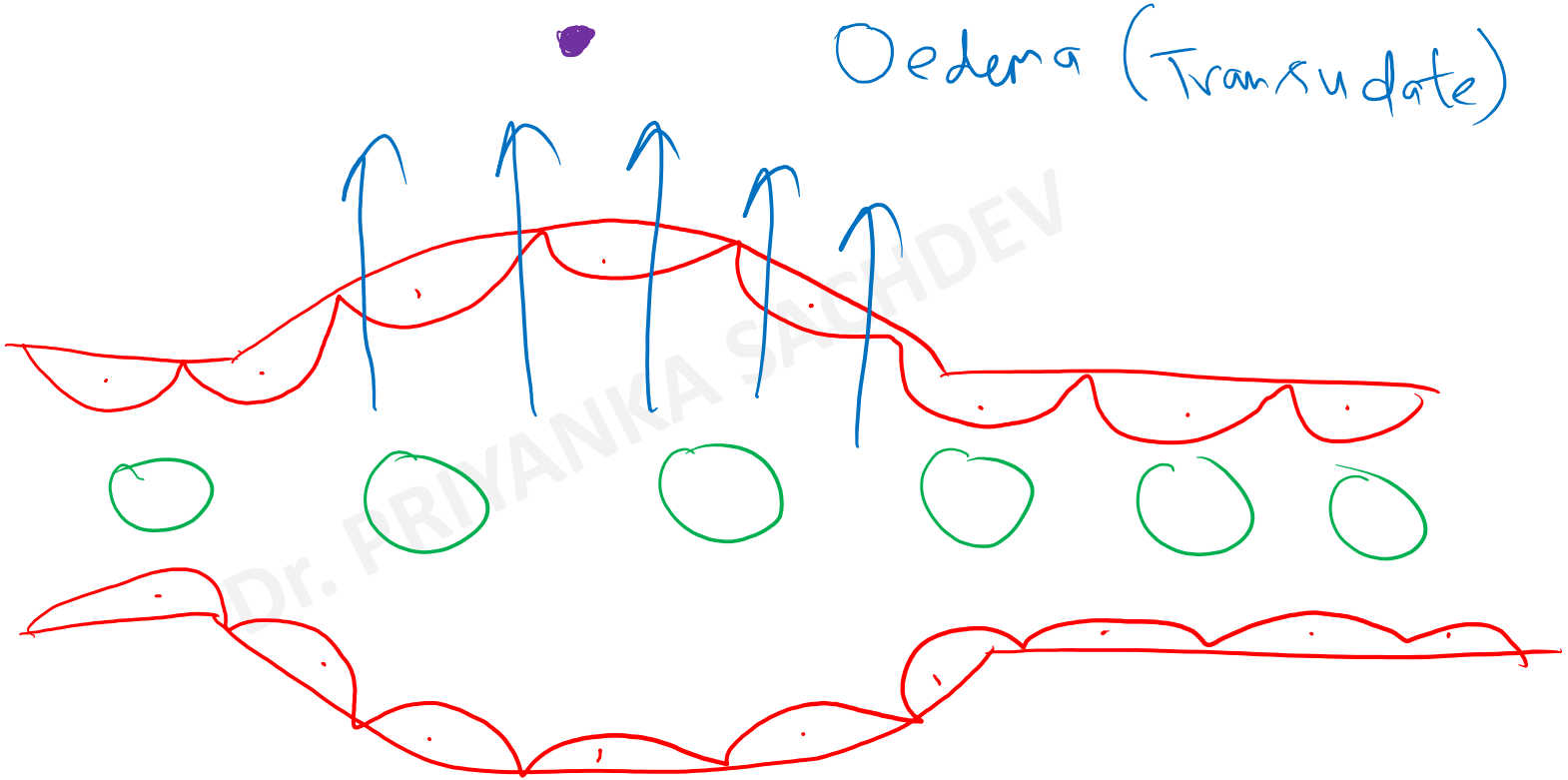
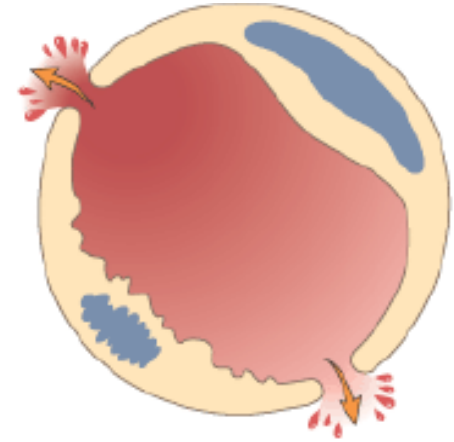
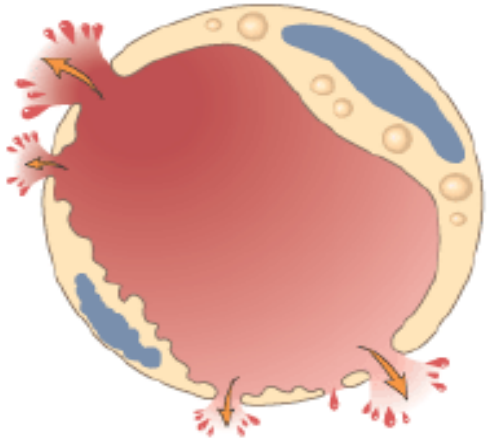
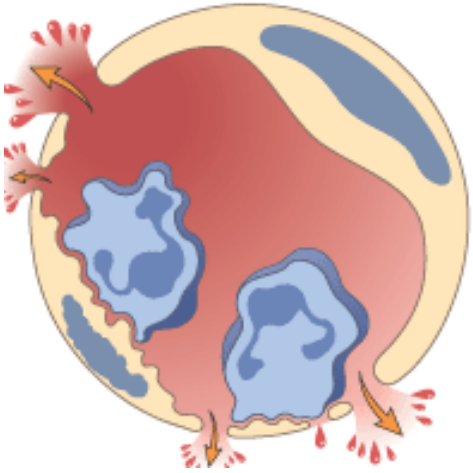


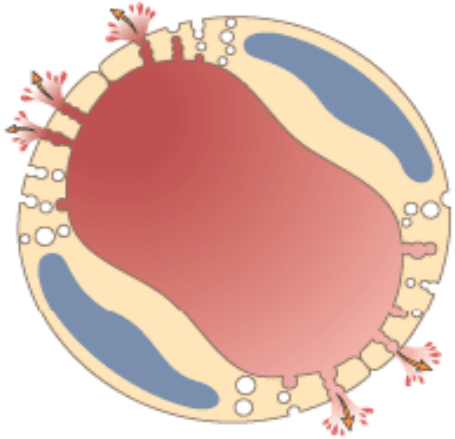


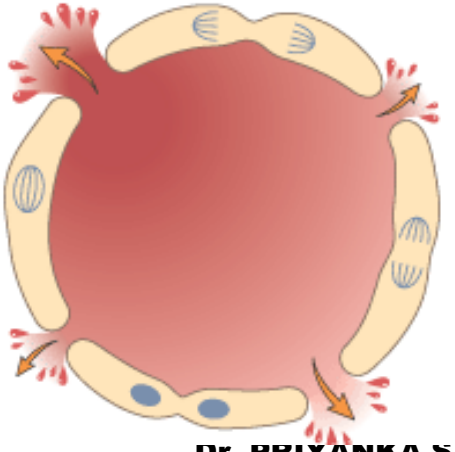


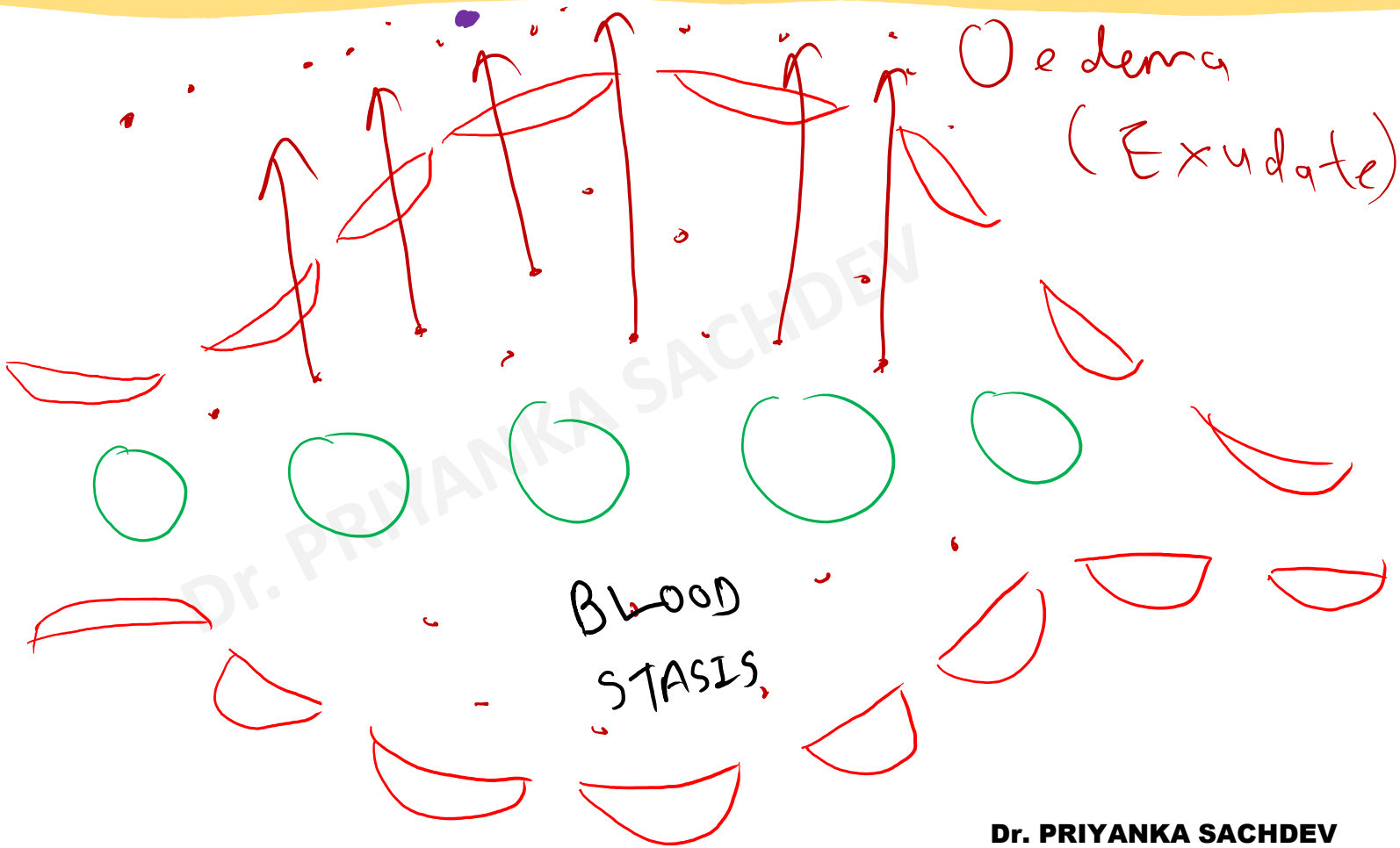


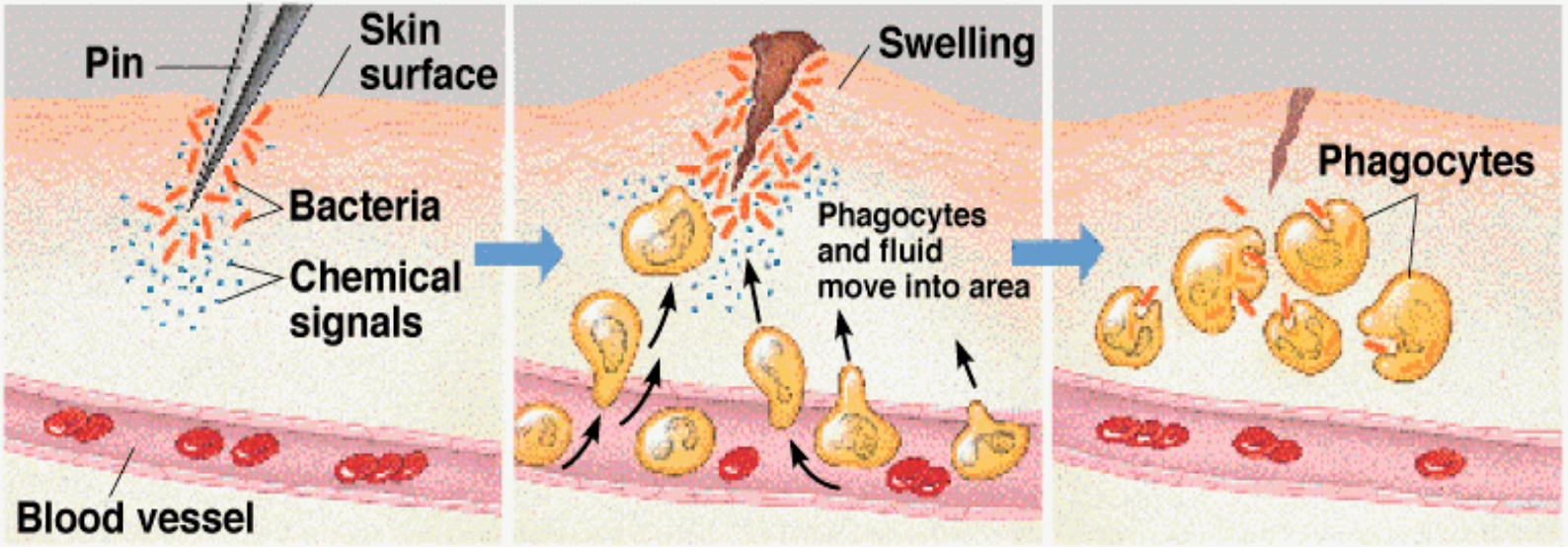










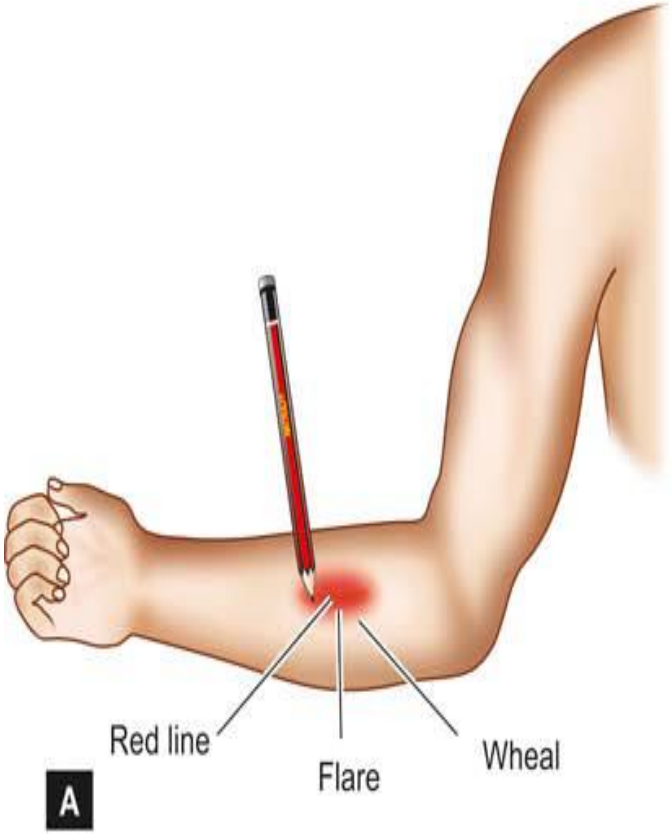


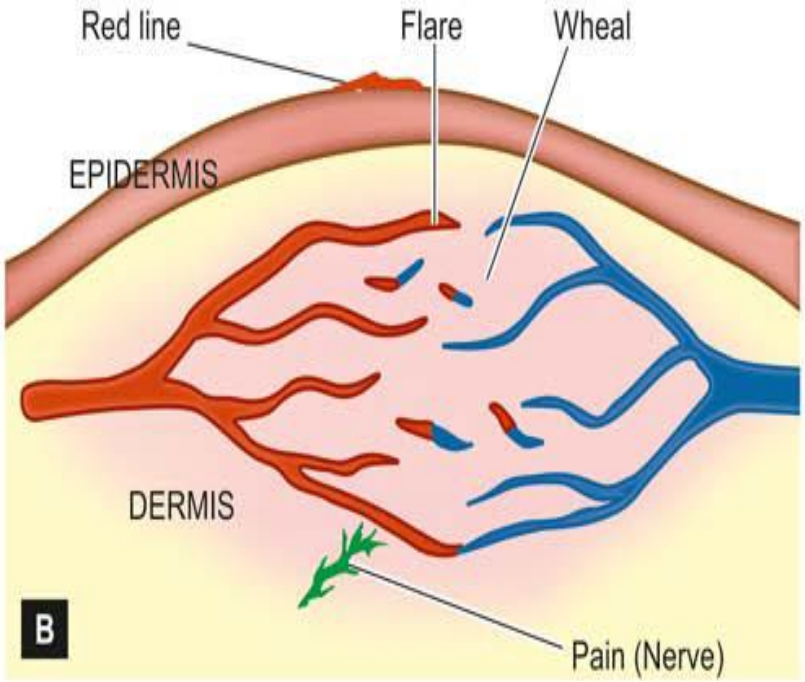
1. Tissue injury; release of chemical signals such as histamine
2. Dilation and increased leakiness of local blood vessels; migration of phagocytes to the area
3. Phagocytes (macrophages and neutrophils) consume bacteria and cell debris; tissue heals

TRIPLE RESPONSE

- Demonstrated by the **Lewis experiment**
- Lewis induced the **changes in the skin of inner aspect of forearm by firm stroking with a blunt point.**

- The reaction elicited is known as **triple response or red line response**





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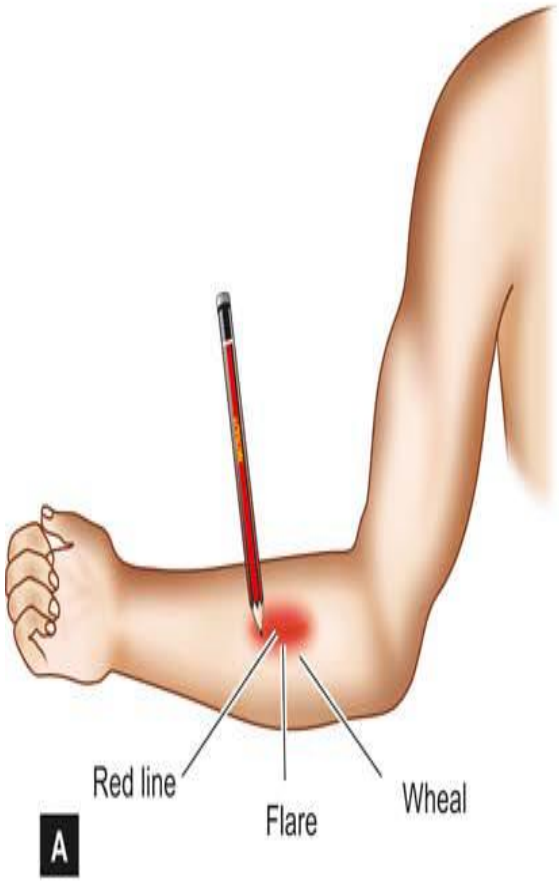
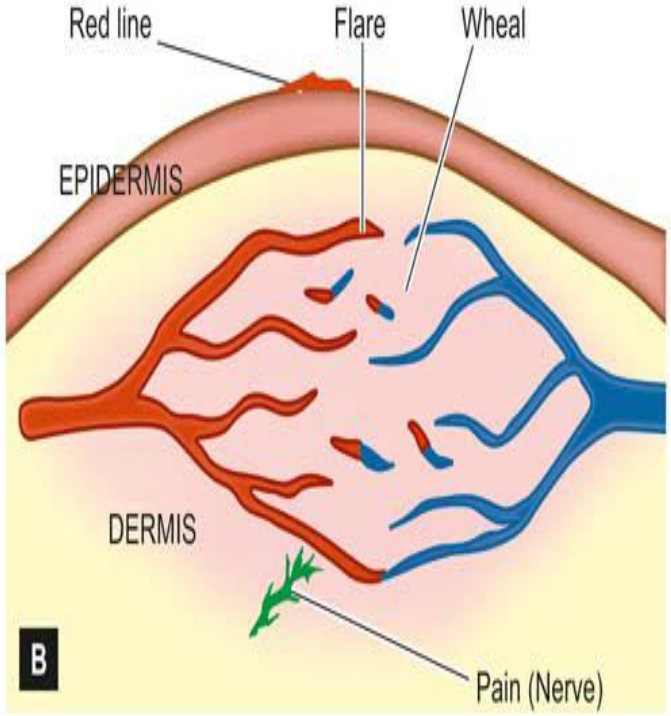
TRIPLE RESPONSE

- i) **Red line** due to local **vasodilatation of capillaries and venules.**
- ii) **Flare** is the bright reddish surrounding the red line and results from **vasodilatation of the adjacent arterioles**
- iii) **Wheal** is the swelling due to **transudation of fluid into the extravascular space**


Red line
Flare
Wheal
A


Red line
Flare
Wheal
EPIDERMIS
DERMIS
Pain (Nerve)
B

SACHDEV

POLLS 2

Scan or Click to watch Cell Adaptation & Injury

Scan or Click to watch Apoptosis & Necrosis

Scan or Click to watch Inflammation

Scan or Click to watch Haemodynamic Disorder

Sequence of events in acute inflammation -

- a) Vasodilatation -> Stasis -> Transient vasoconstriction -> Increased permeability
- b) Transient vasoconstriction -> Stasis -> Vasodilatation -> Increased permeability
- c) Transient vasoconstriction Vasodilatation -> Stasis -> Increased permeability
- d) Transient vasoconstriction -> Vasodilatation -> Increased permeability -> Stasis

Sequence of events in acute inflammation -

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- c) Transient vasoconstriction Vasodilatation -> Stasis -> Increased permeability
- d) Transient vasoconstriction -> Vasodilatation -> Increased permeability -> Stasis

In acute inflammation due to the contraction of endothelial cell cytoskeleton, which of the following results-

- a) Delayed transient increase in permeability
- b) Early transient increase in permeability
- c) Delayed permanent increase in permeability
- d) Early permanent increase in permeability

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- a) Delayed transient increase in permeability
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Increased permeability in acute inflammation is due to –

- a) Histamine
- b) IL-2
- c) TGF-J3
- d) FGF

Increased permeability in acute inflammation is due to –

- a) Histamine
- b) IL-2
- c) TGF-J3
- d) FGF

Most characteristic feature of acute inflammation

a) Vasoconstriction
b) Vascular stasis
c) Increased vascular permeability
d) Margination of leucocytes

Most characteristic feature of acute inflammation

a) Vasoconstriction

b) Vascular stasis

c) Increased vascular permeability

d) Margination of leucocytes

First to appear in acute inflammation

a) Vasodilatation
b) Vasoconstriction
c) Increased vascular permeability
d) Decreased vascular permeability

First to appear in acute inflammation

a) Vasodilatation

b) Vasoconstriction

c) Increased vascular permeability

d) Decreased vascular permeability

Rubor in inflammation is due to -

a) Dilation of arterioles
b) Increased vascular permeability
c) Increased viscocity of blood
d) Edema

A

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All of the following vascular changes are observed in acute inflammation, except-

a) Vasodilation
b) Stasis of blood
c) Increased vascular permeability
d) Decreased hydrostatic pressure

D

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The following host tissue responses can be seen in acute inflammation, except -

a) Exudation
b) Vasodilation
c) Margination
d) Granuloma formation

D

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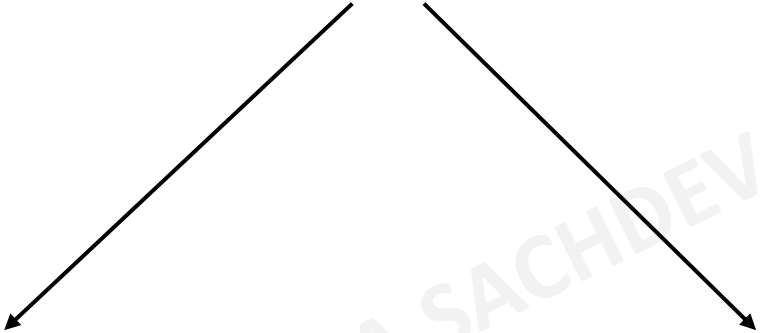
Acute inflammation



Vascular events

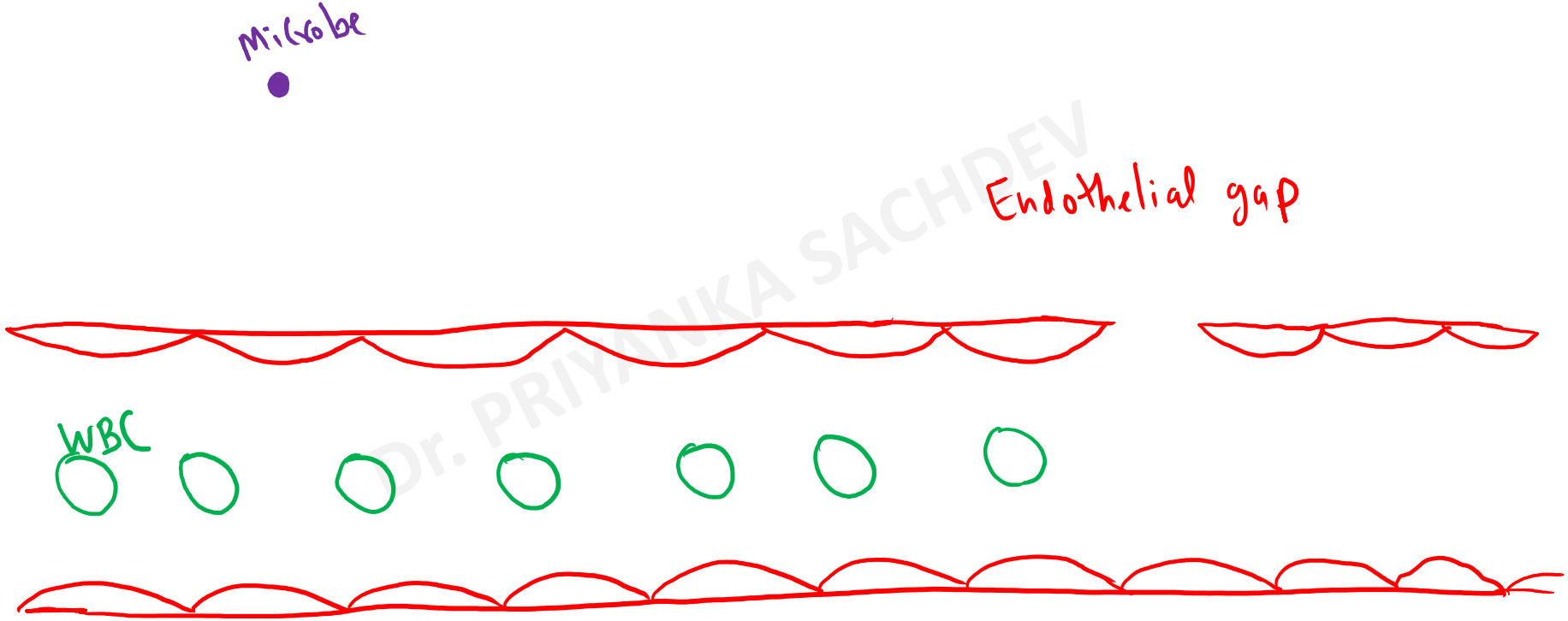
Cellular reaction

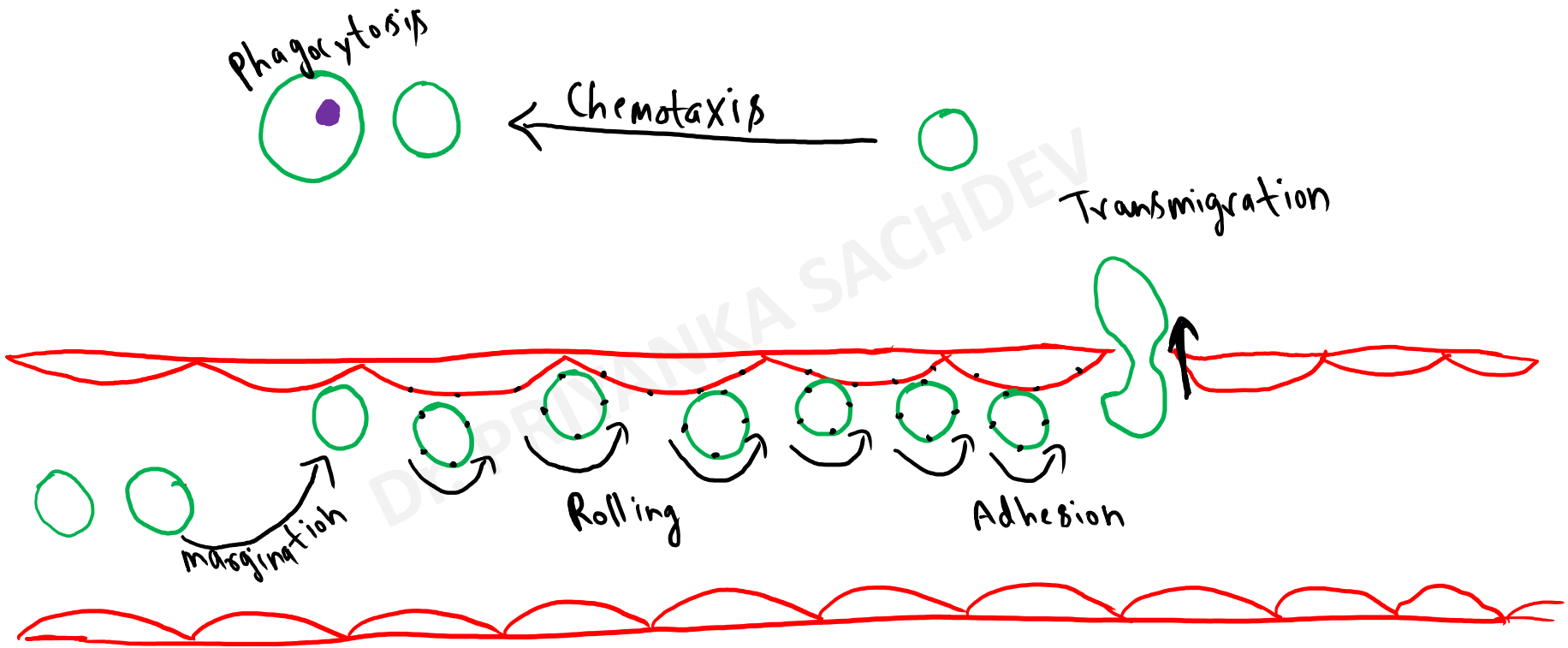
Cellular events

The main function of the increased vascular permeability and stasis is to **deliver leucocytes at the site of injury**

Cellular events

1. Margination and pavementing
2. Rolling
3. Adhesion
4. Transmigration (diapedes)
5. Chemotaxis
6. Phagocytosis





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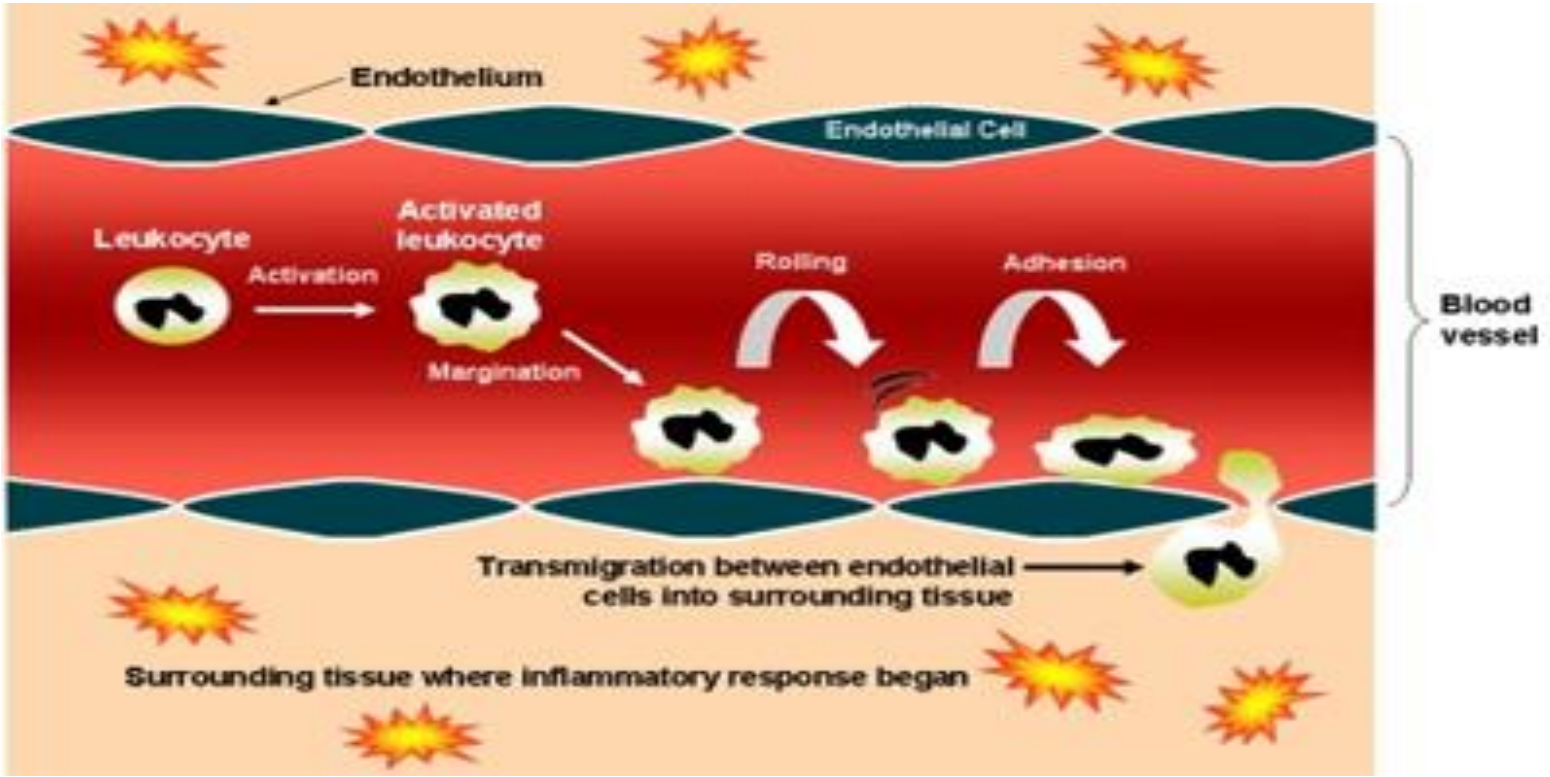
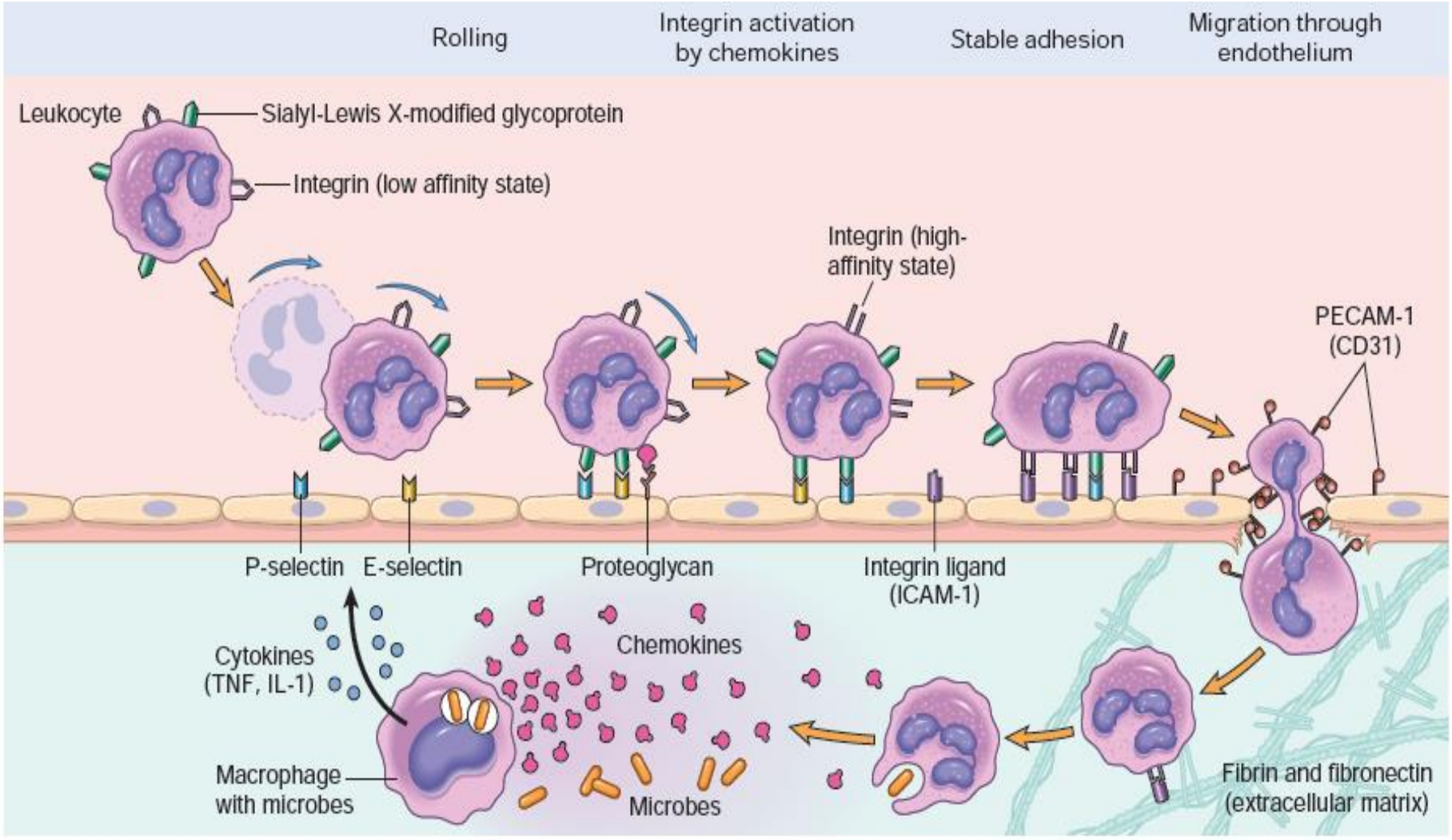

Endothelium
Endothelial Cell
Leukocyte
Activation
Activated leukocyte
Margination
Rolling
Adhesion
Blood vessel
Transmigration between endothelial cells into surrounding tissue
Surrounding tissue where inflammatory response began


Rolling
Integrin activation by chemokines
Stable adhesion
Migration through endothelium
Leukocyte
Sialyl-Lewis X-modified glycoprotein
Integrin (low affinity state)
Integrin (high-affinity state)
PECAM-1 (CD31)
P-selectin
E-selectin
Proteoglycan
Integrin ligand (ICAM-1)
Cytokines (TNF, IL-1)
Chemokines
Macrophage with microbes
Microbes
Fibrin and fibronectin (extracellular matrix)

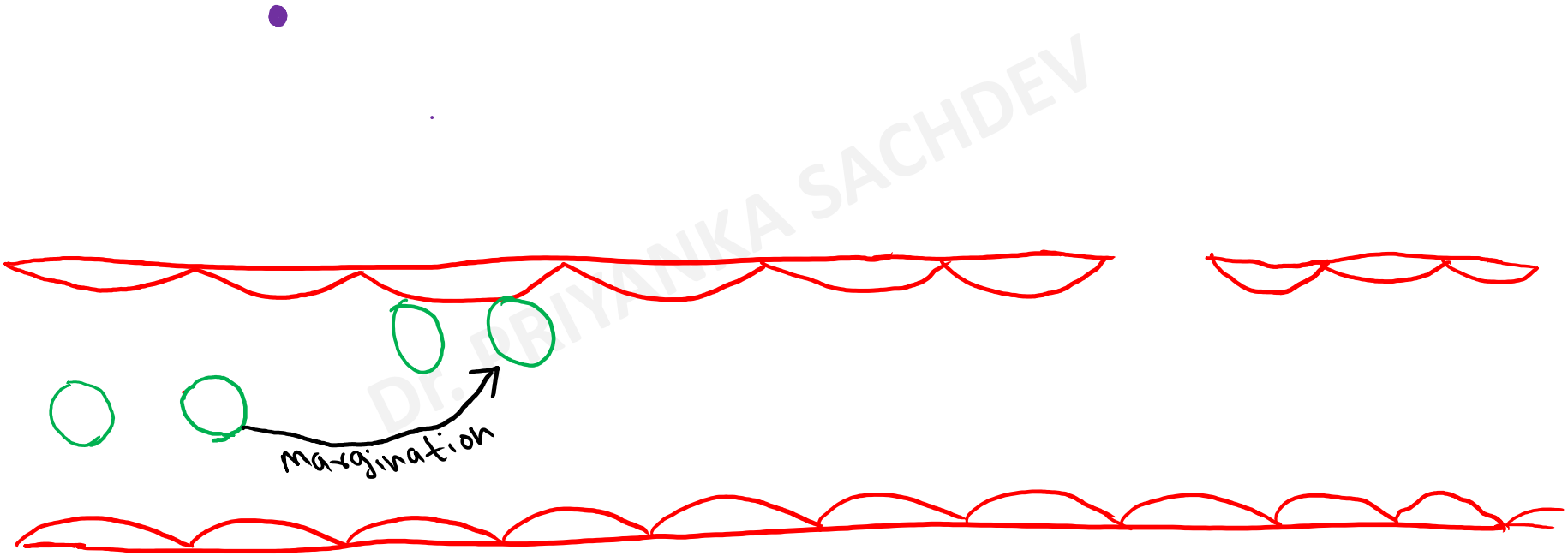
Cellular events

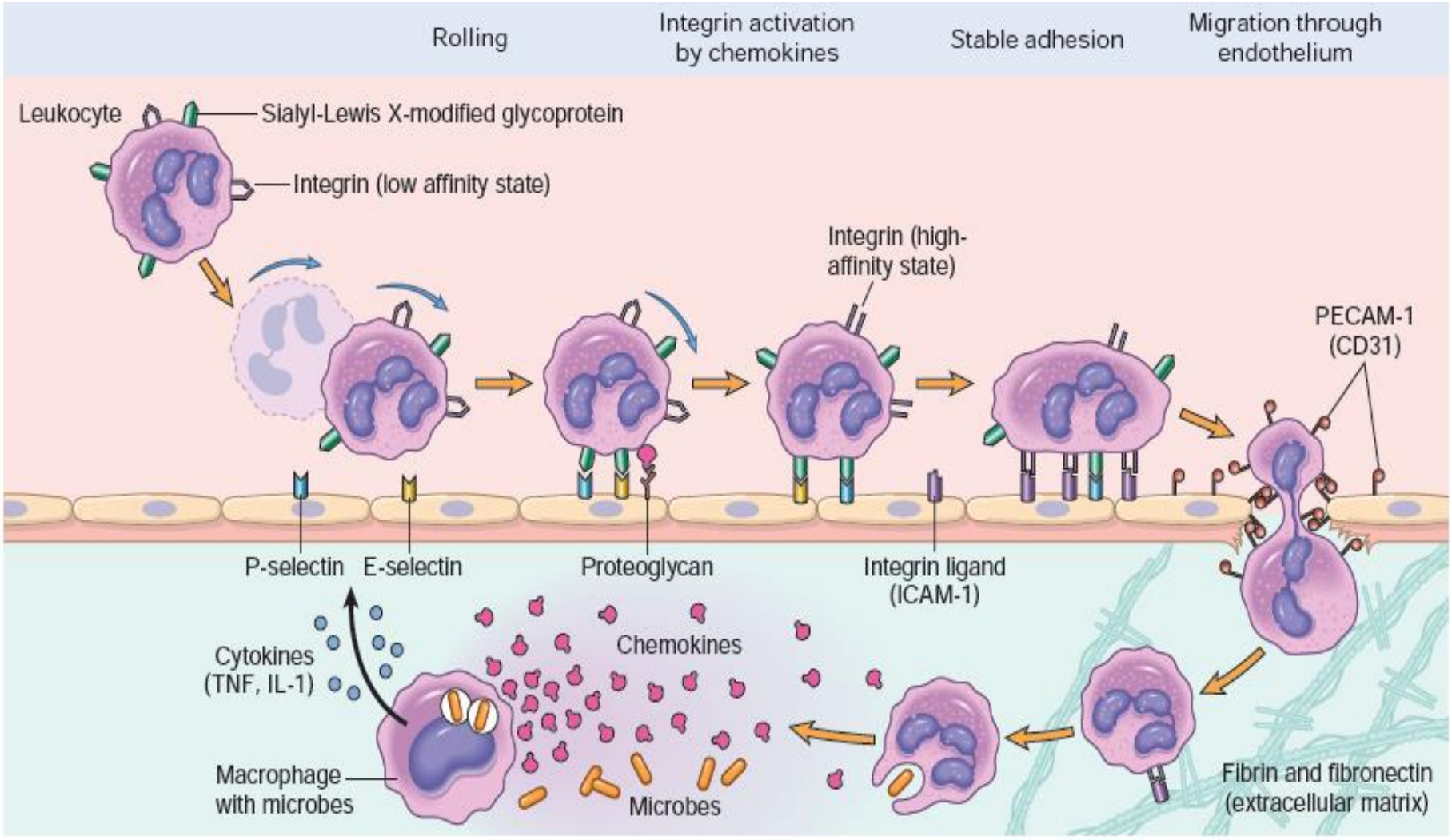
1. Margination and pavementing
2. Rolling
3. Adhesion
4. Transmigration (diapedes)
5. Chemotaxis
6. Phagocytosis

MARGINATION

- **The normal axial flow** consists of central stream of cells comprised by leucocytes and RBCs and peripheral cell-free layer of plasma close to vessel wall.

- **WBCs leave the centre and comes at periphery of blood vessel→ Reversal of axial blood flow**

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Chemokines
Macrophage with microbes
Microbes
Fibrin and fibronectin (extracellular matrix)

1.slowing and stasis

Central stream of cells widens

↓

2.Loss of plasma by exudation

Peripheral plasma zone becomes narrower

↓

As a result of this redistribution

↓

Neutrophils of the central column come close to the vessel wall

↓

Reversal of axial blood flow

↓

Margination and pavementing

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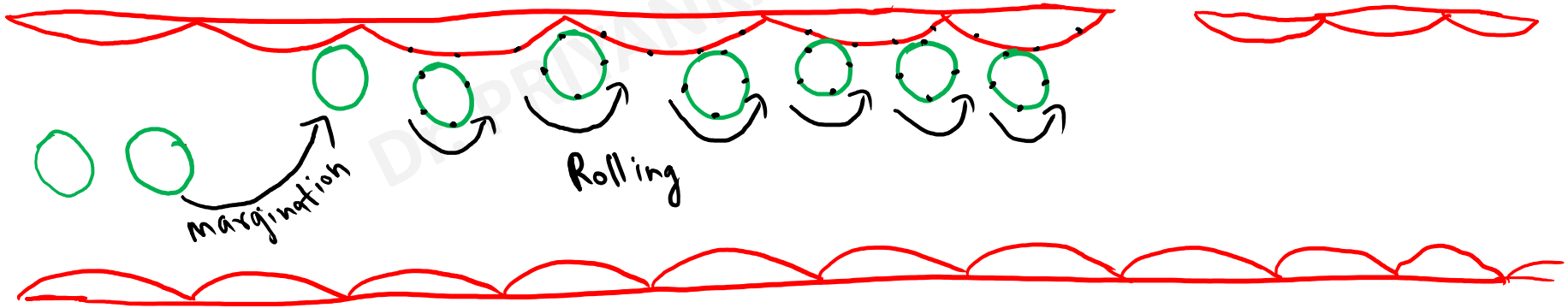
- The endothelium can be virually lined by white cells called **Pavementing**

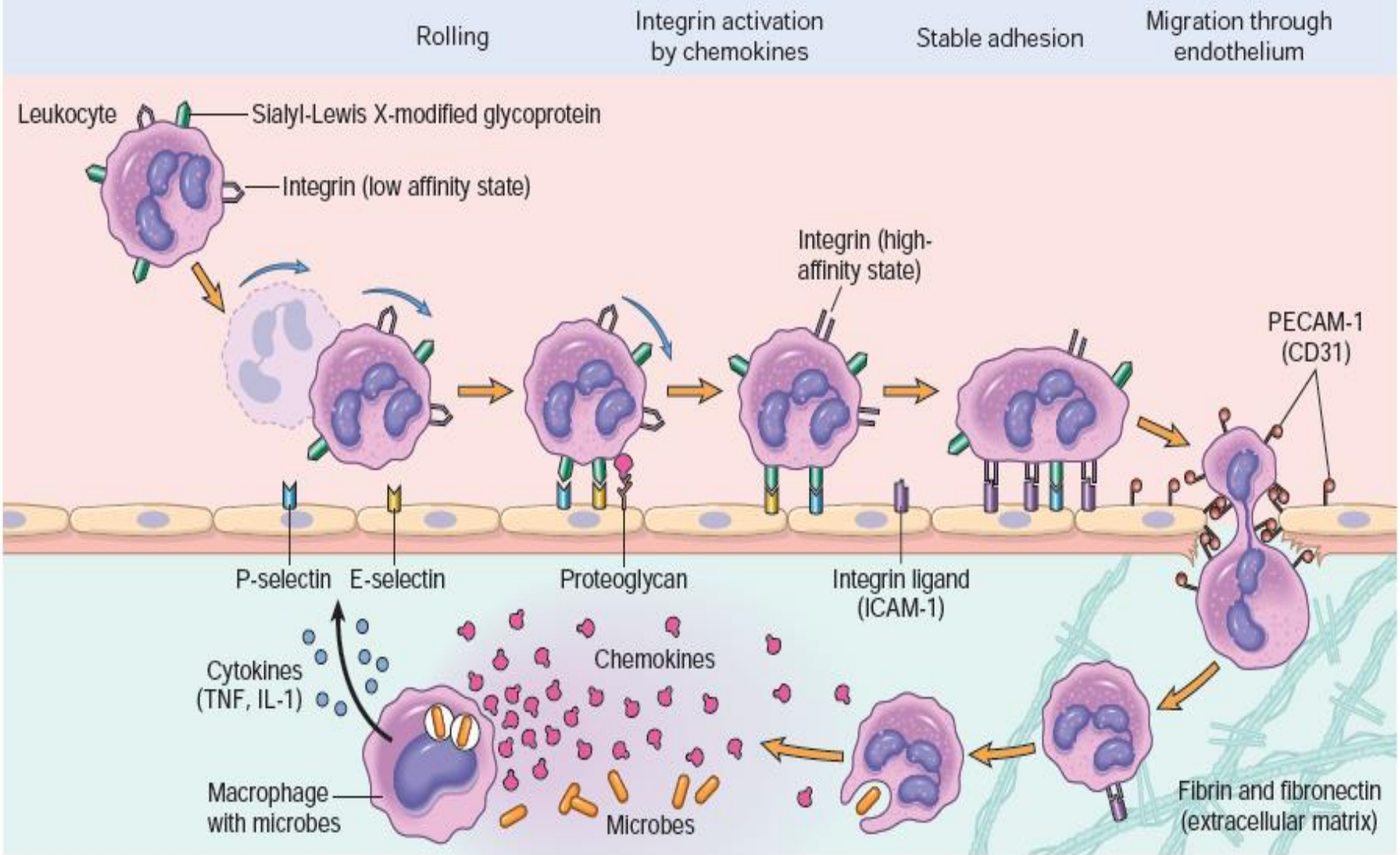
Cellular events

1. Margination and pavementing
2. Rolling
3. Adhesion
4. Transmigration (diapedes)
5. Chemotaxis
6. Phagocytosis

ROLLING

- Peripherally marginated and pavemented neutrophils slowly roll over the endothelial cells lining the vessel wall due to **transient bonds** between them → **Rolling**

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Cytokines (TNF, IL-1)
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Macrophage with microbes
Microbes
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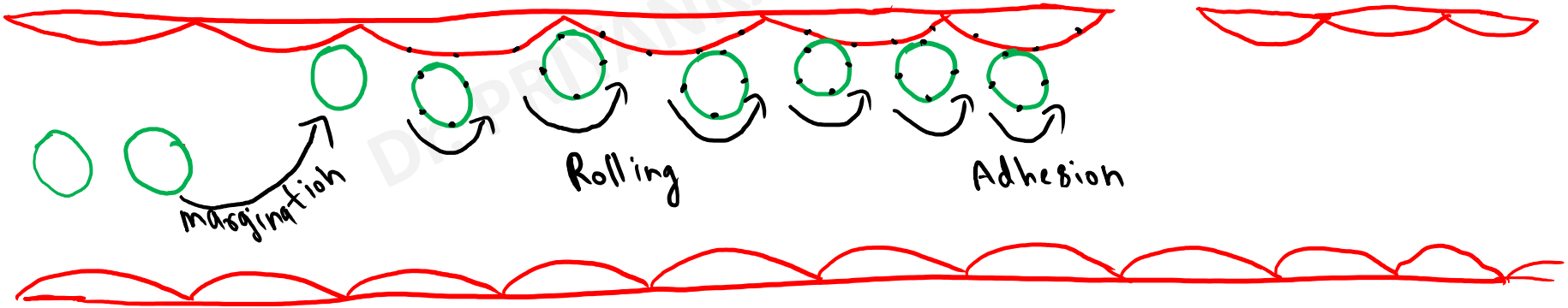
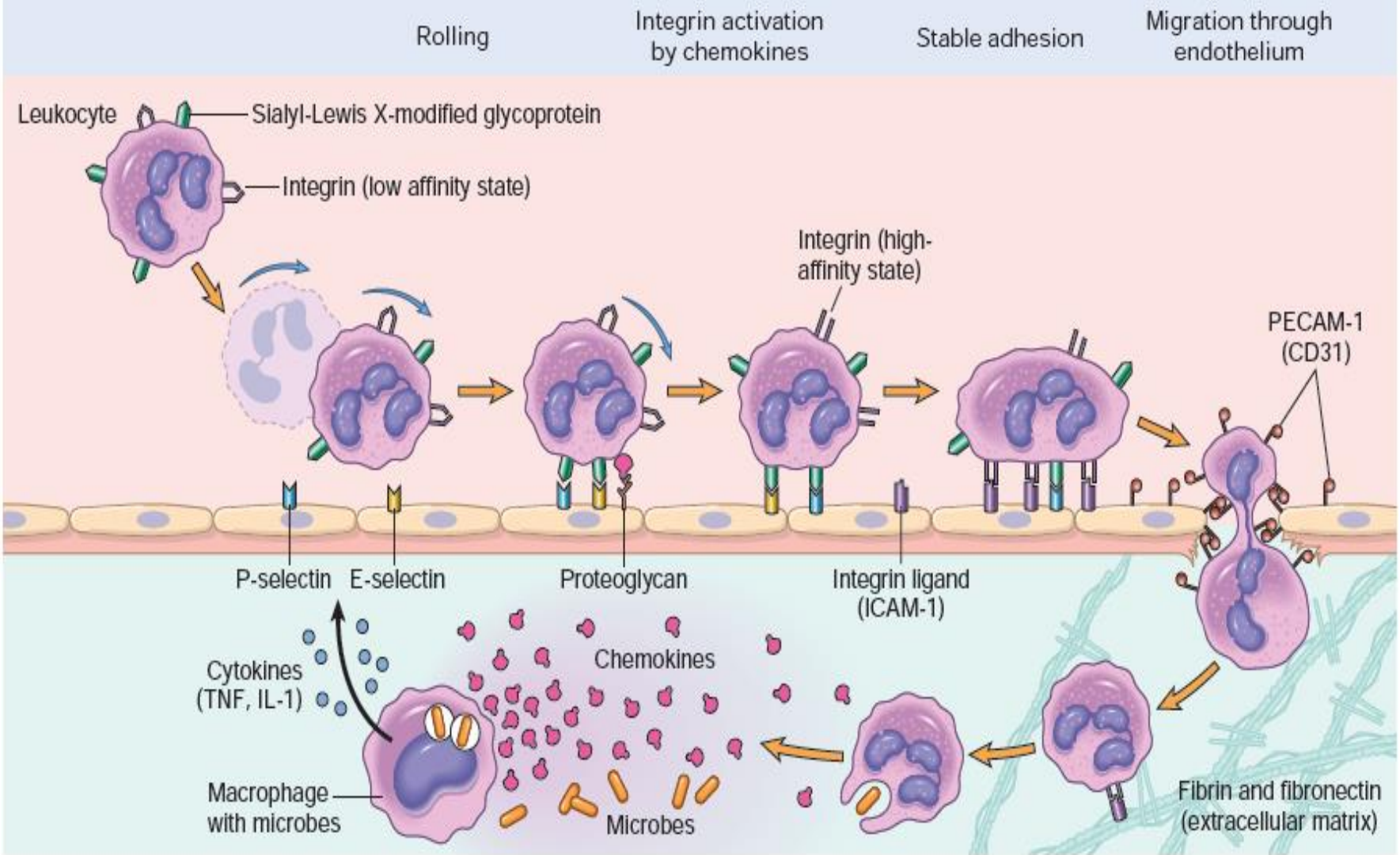
ADHESION

- This is followed by transient bond between the leucocytes and endothelial cells becoming **firmer** → **Adhesion**

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Mechanism of rolling and adhesion

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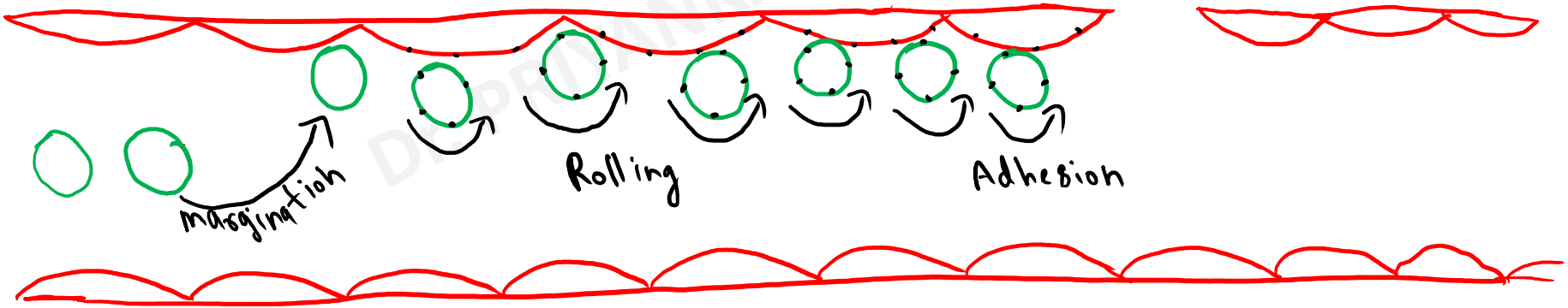
Complementary adhesion molecules (CAM)

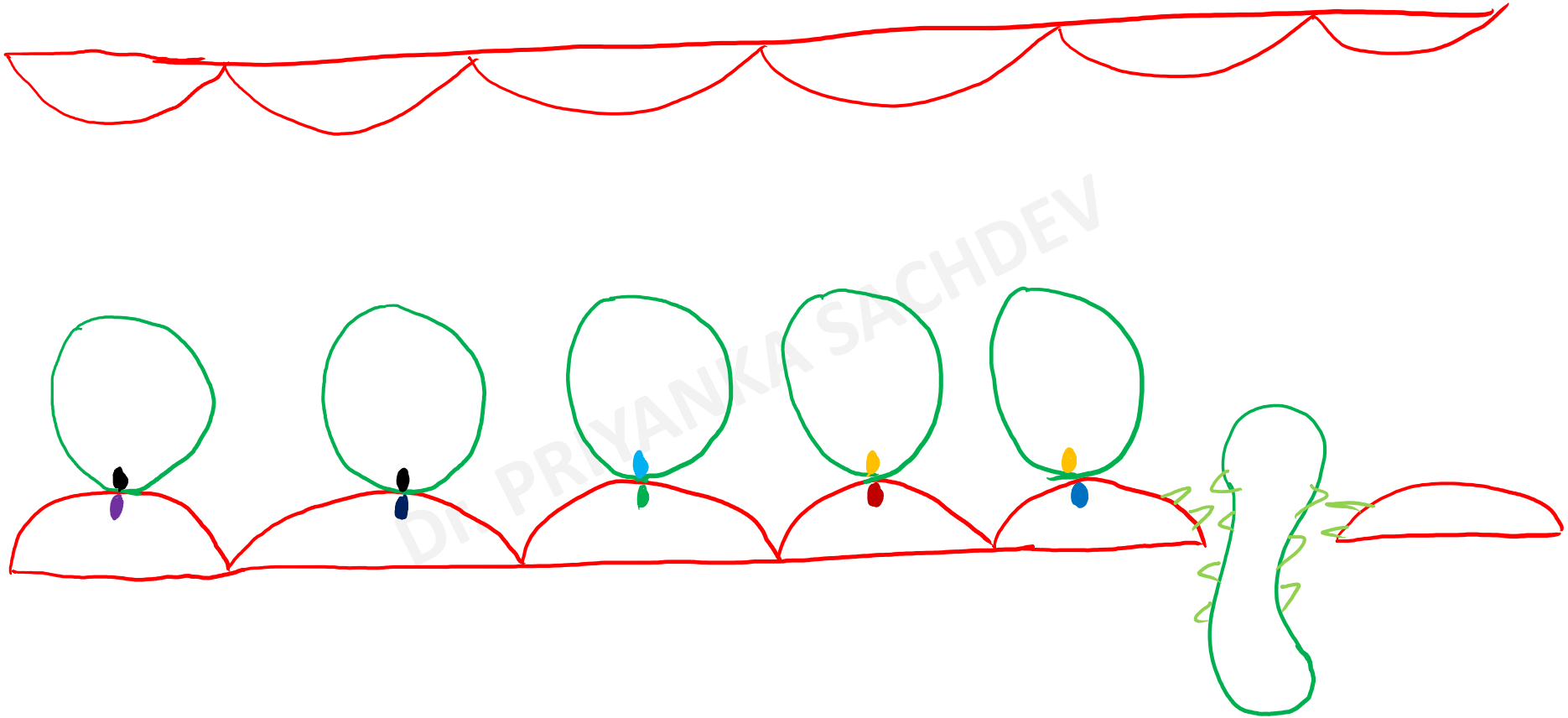
- The attachment of leukocytes to endothelial cells is mediated by complementary adhesion molecules (CAM) on the two cell types

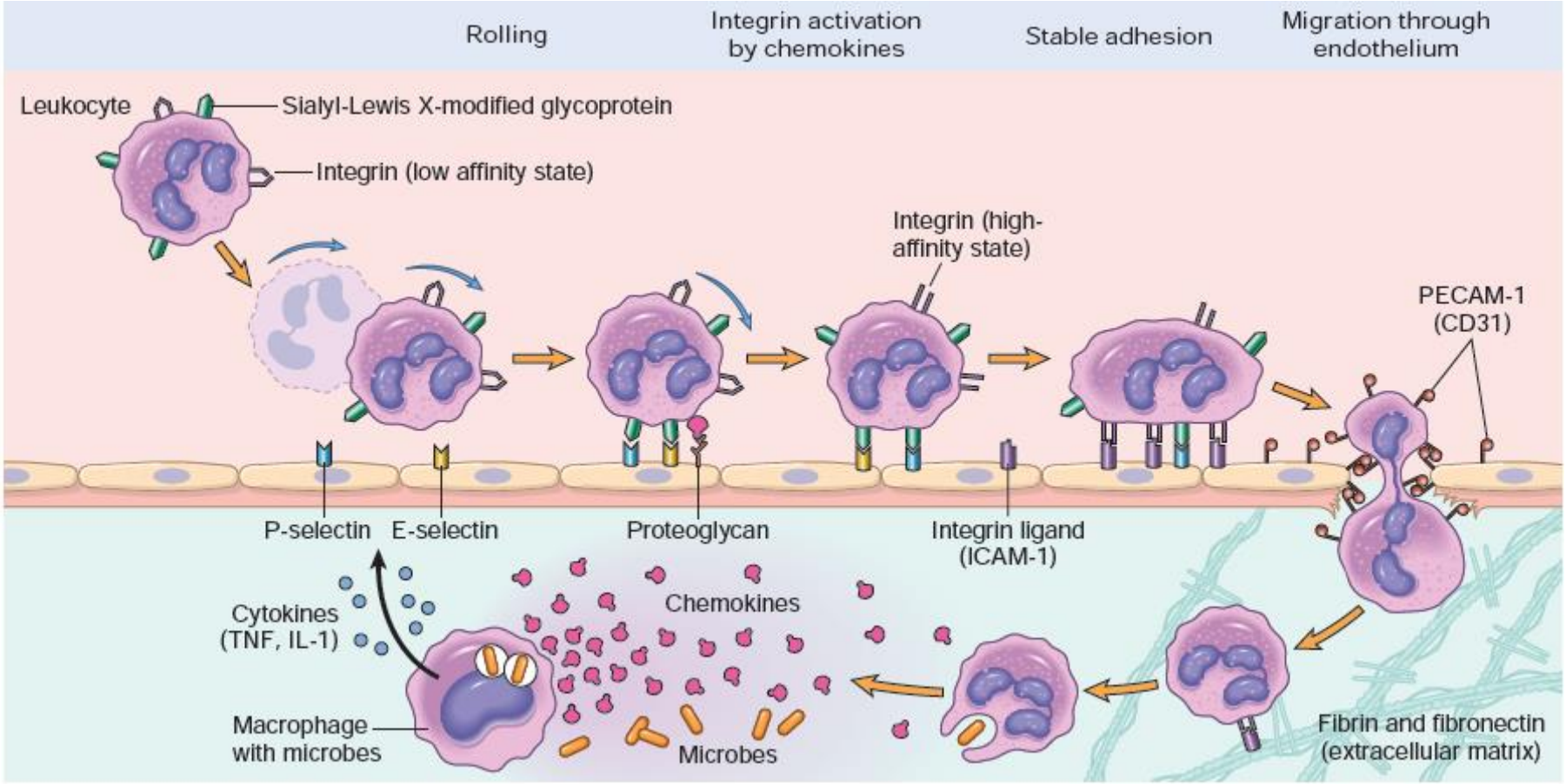
- The following (CAMs) bring about rolling and adhesion phases

Endothelial Molecule	Leukocyte Molecule	Major Role
P-selectin	Sialyl-Lewis X–modified proteins	Rolling (neutrophils, monocytes, T lymphocytes)
E-selectin	Sialyl-Lewis X–modified proteins	Rolling and adhesion (neutrophils, monocytes, T lymphocytes)
GlyCam-1, CD34	L-selectin [1]	Rolling (neutrophils, monocytes)
ICAM-1 (immunoglobulin family)	CD11/CD18 (β_2) integrins (LFA-1, Mac-1)	Adhesion, arrest, transmigration (neutrophils, monocytes, lymphocytes)
VCAM-1 (immunoglobulin family)	VLA-4 (β_1) integrin	Adhesion (eosinophils, monocytes, lymphocytes)

PECAM-1 (CD-31) **PECAM-1 (CD-31 [AI 15])** **Diapedesis [AIIMS 14] (transmigration)**







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PECAM-1 (CD-31) **PECAM-1 (CD-31 [AI 15])** **Diapedesis [AIIMS 14] (transmigration)**

REMEMBER

- **P selectins** (CD-62 P) - endothelial cells and platelets, involved in rolling.
- **E selectin** (CD-62 E) - endothelial cells, associated with both rolling and adhesion.
- **L selectin** (CD-62 L) - lymphocytes and neutrophils, responsible for rolling.

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PECAM-1 (CD-31) **PECAM-1 (CD-31 [AI 15])** **Diapedesis [AIIMS 14] (transmigration)**

REMEMBER

- **P and L selectin** are involved in rolling

- **E-selectin** is involved in rolling and adhesion

- **Intercellular adhesion molecule-1 (ICAM-1, also called CD54)** on endothelial cell

- **Vascular cell adhesion molecule-1 (VCAM-1, also named CD106)** on endothelial cell

- **Platelet-endothelial cell adhesion molecule-1 (PECAM-1) or CD31** on both endothelial cell and leucocyte, involved in leucocyte migration from the endothelial surface.

Endothelial Molecule	Leukocyte Molecule	Major Role
P-selectin	Sialyl-Lewis X–modified proteins	Rolling (neutrophils, monocytes, T lymphocytes)
E-selectin	Sialyl-Lewis X–modified proteins	Rolling and adhesion (neutrophils, monocytes, T lymphocytes)
GlyCam-1, CD34	L-selectin [1]	Rolling (neutrophils, monocytes)
ICAM-1 (immunoglobulin family)	CD11/CD18 (β_2) integrins (LFA-1, Mac-1)	Adhesion, arrest, transmigration (neutrophils, monocytes, lymphocytes)
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Cellular events

1. Margination and pavementing
2. Rolling
3. Adhesion
4. Transmigration (diapedes)
5. Chemotaxis
6. Phagocytosis

TRANSMIGRATION (diapedes)

- Escape out into the extravascular space; this is known as **transmigration**

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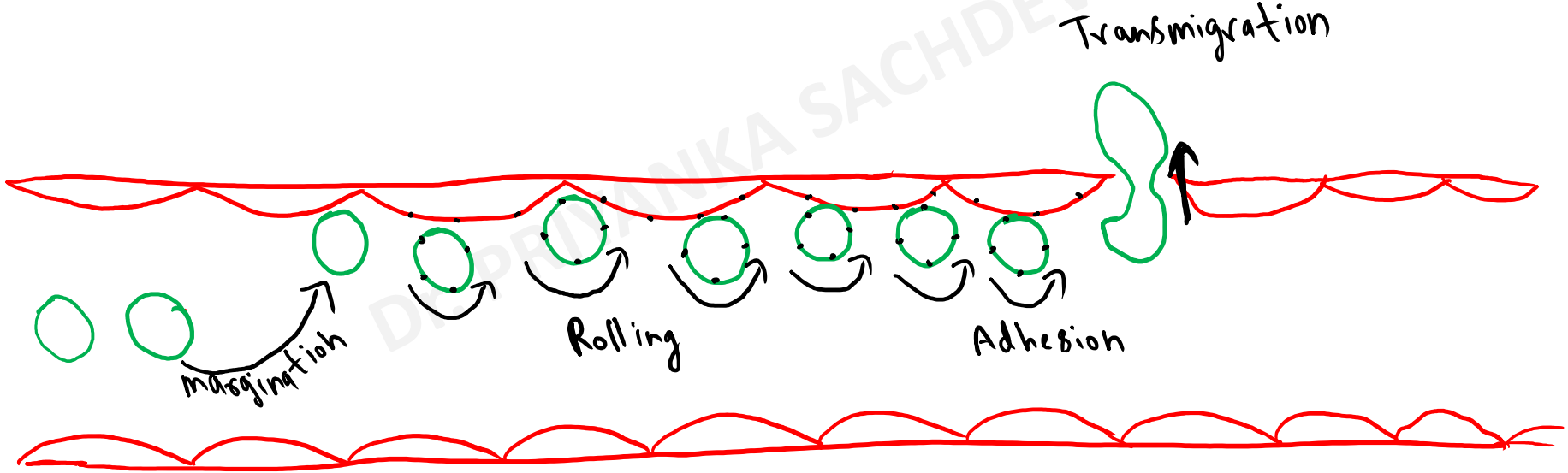

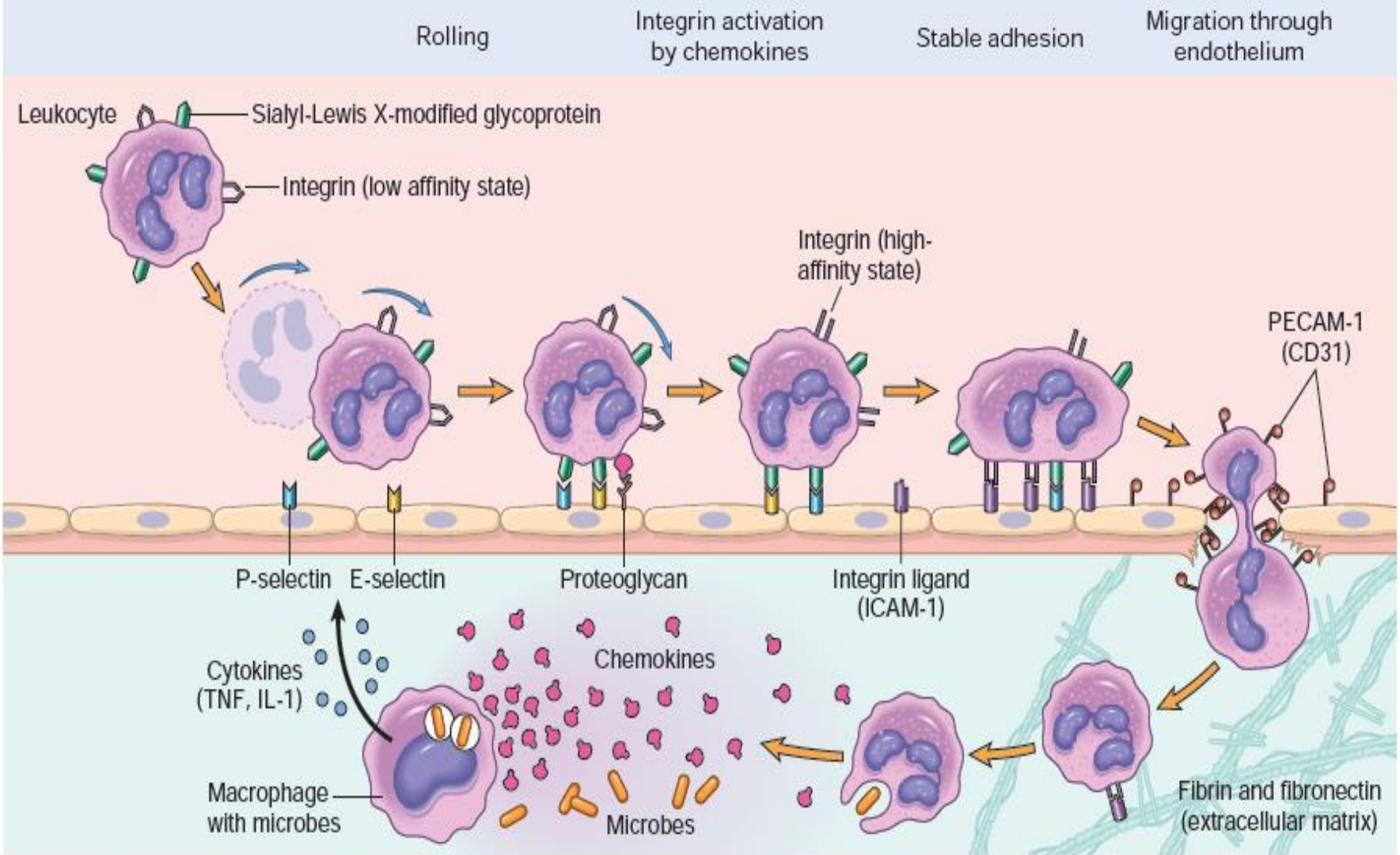
Rolling
Integrin activation by chemokines
Stable adhesion
Migration through endothelium
Leukocyte
Sialyl-Lewis X-modified glycoprotein
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Integrin (high-affinity state)
PECAM-1 (CD31)
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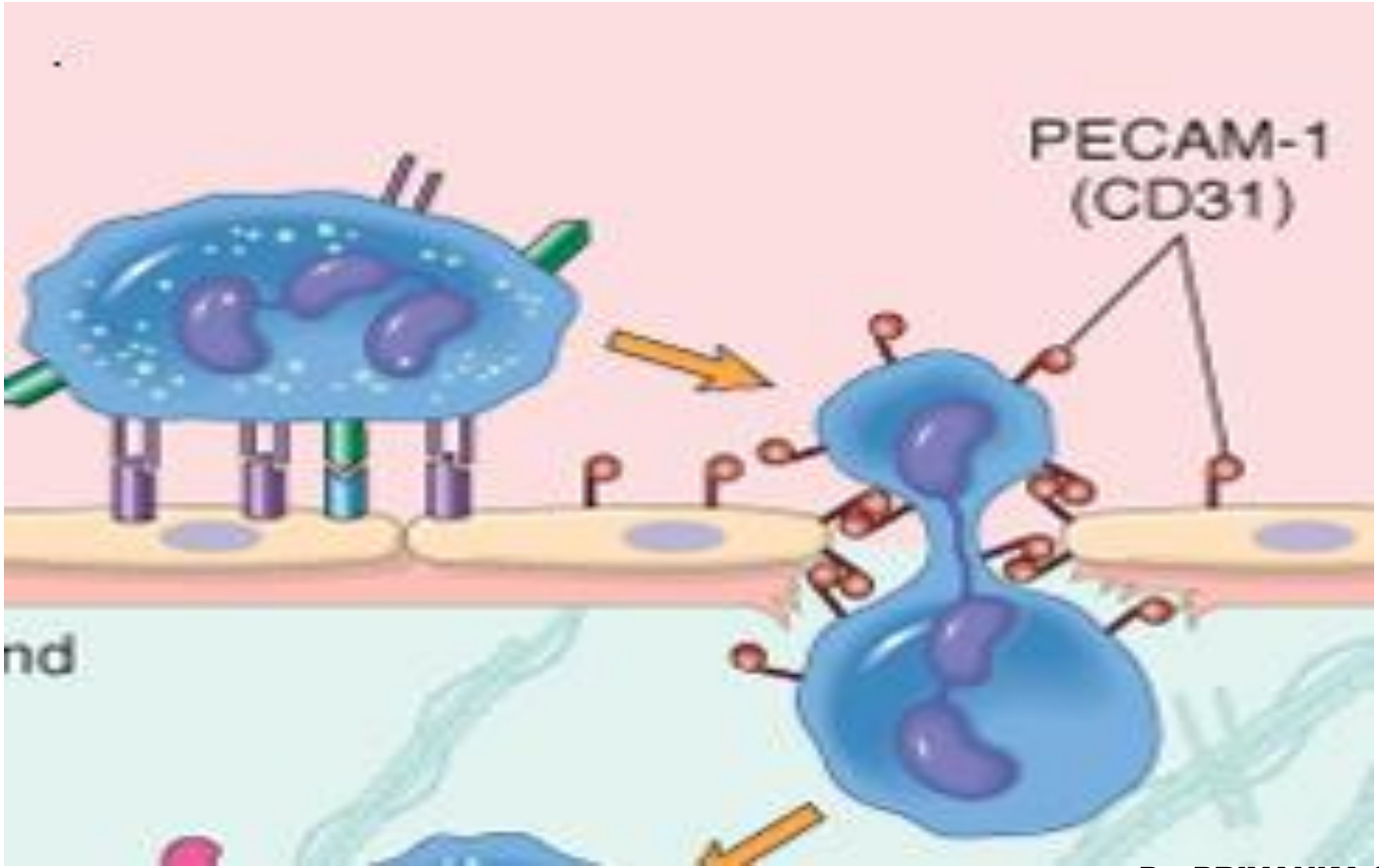
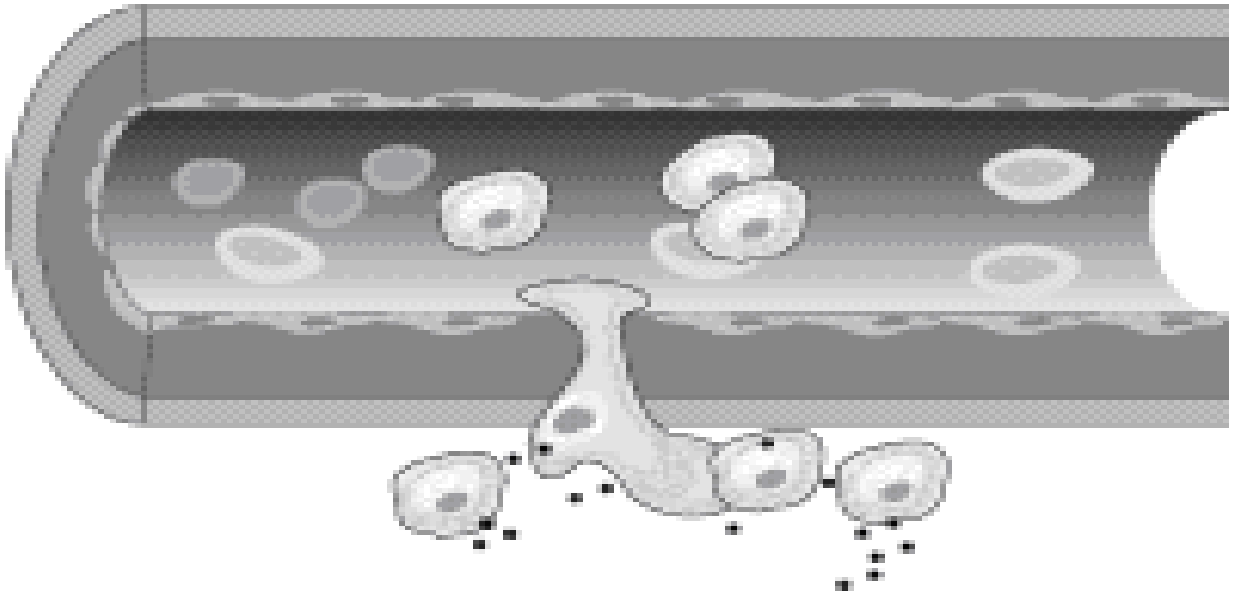
Proteoglycan
Integrin ligand (ICAM-1)
Cytokines (TNF, IL-1)
Chemokines
Macrophage with microbes
Microbes
Fibrin and fibronectin (extracellular matrix)


PECAM-1
(CD31)
nd



migration of white blood cells out of blood vessel and release of white blood cell chemicals

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After sticking of neutrophils to endothelium they move along the endothelial surface till a suitable site between the endothelial cells is found where the neutrophils throw out **cytoplasmic pseudopods**

↓

the neutrophils **lodged** between the endothelial cells and basement membrane

↓

cross the basement membrane by damaging it with secreted **collagenases**

↓

Escape out into the extravascular space; this is known as **transmigration**

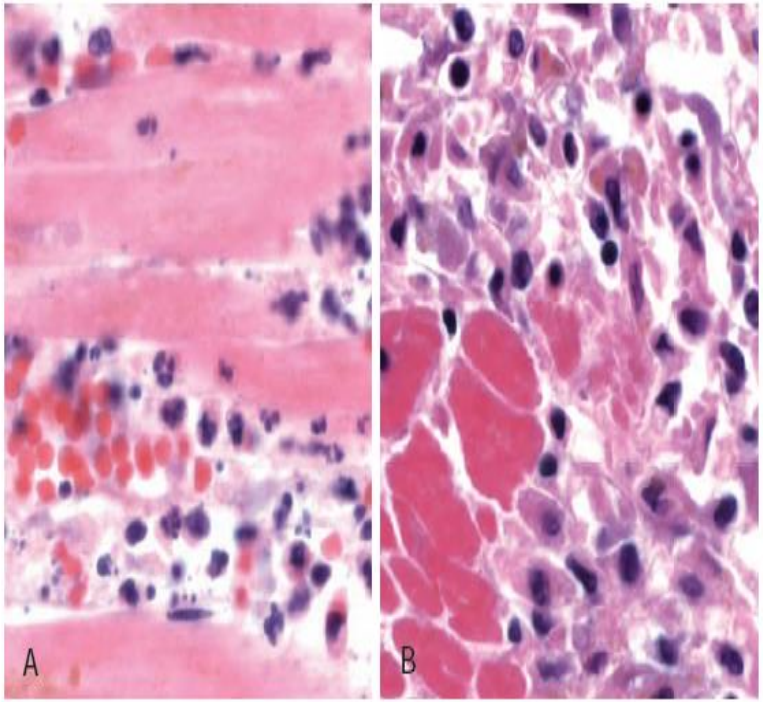
- Simultaneous to emigration of leucocytes, escape of **red cells** through gaps between the endothelial cells,This is known as **diapedesis**

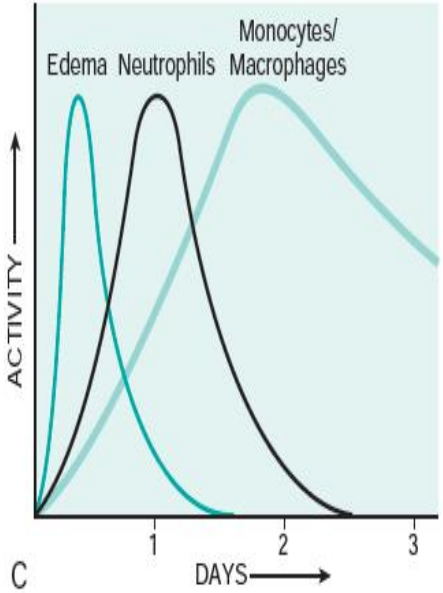
- It is a **passive phenomenon**

- **PECAM**

REMEMBER

- **Neutrophils** are the dominant cell in the **first 24 hours**
- **Monocyte-macrophages** appear in the next **24-48 hours**
- However, neutrophils are short-lived (24-48 hours) while monocyte-macrophages survive much longer.


A
B

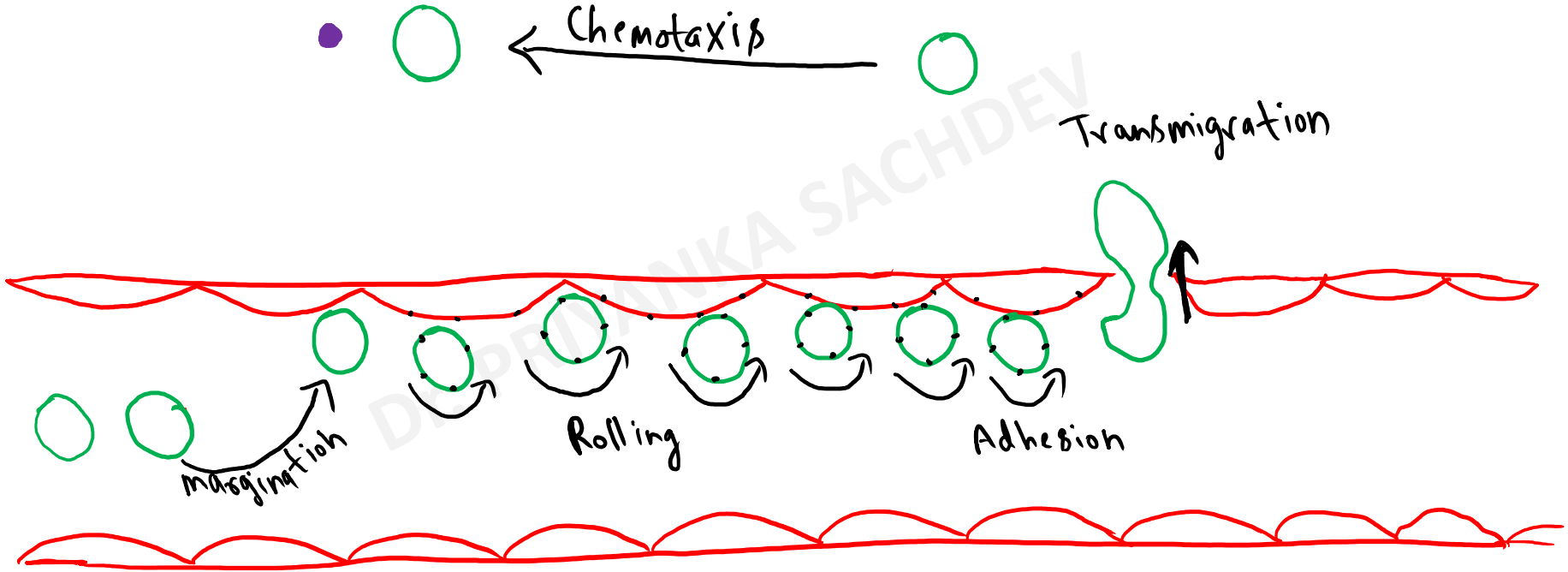

Edema
Neutrophils
Monocytes/
Macrophages
ACTIVITY
1
2
3
DAYS
C

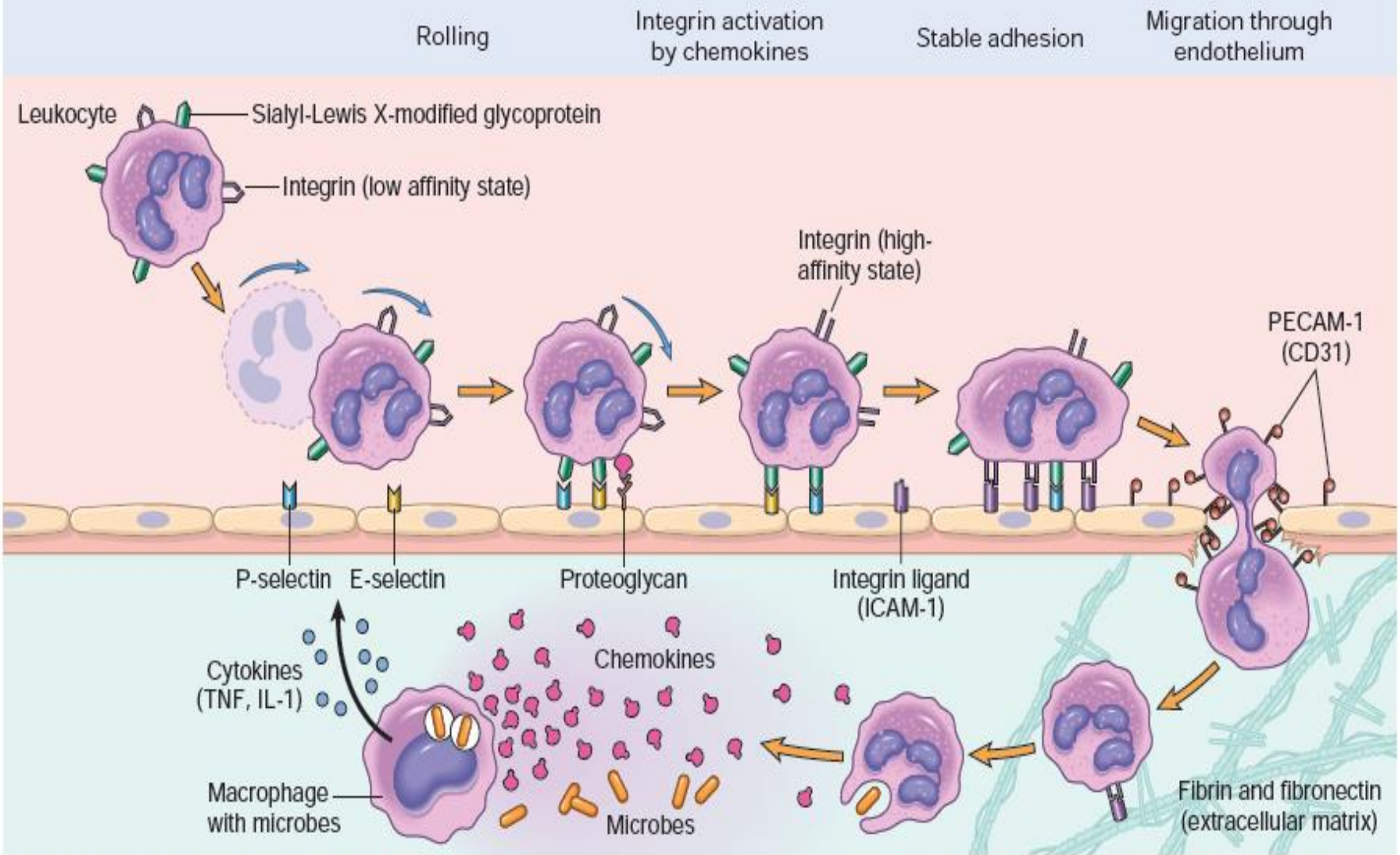
Cellular events

1. Margination and pavementing
2. Rolling
3. Adhesion
4. Transmigration (diapedes)
5. Chemotaxis
6. Phagocytosis

CHEMOTAXIS

- **Unidirectional** oriented along a chemical gradient.

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Proteoglycan
Integrin ligand (ICAM-1)
Cytokines (TNF, IL-1)
Chemokines
Macrophage with microbes
Microbes
Fibrin and fibronectin (extracellular matrix)

Potent chemotactic substance

- i) Leukotriene B4 **(LT-B4)**
- ii) Components of complement system **(C5a and C3a)**
- iii) Cytokines **(Interleukins, in particular IL-8)**
- iv) Soluble bacterial products (such as formylated peptide)

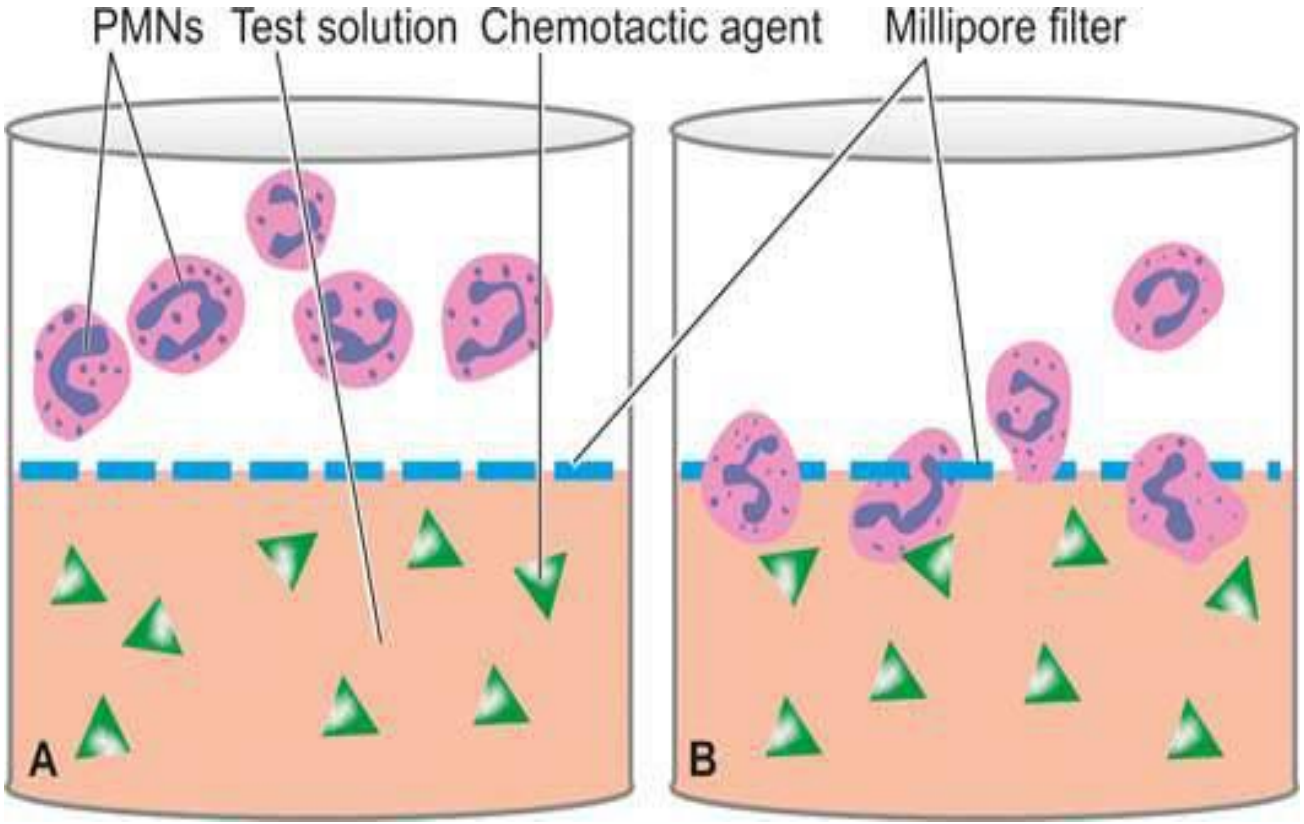
- **C5a is the most powerful chemoattractant (chemokine)**

- **Locomotion in chemotaxis requires polymerization (assembly) of actin**

Boyden's chamber experiment

1. A millipore filter (3 µm pore size) separates the suspension of leucocytes from the test solution containing chemotactic agent.

2. **Leucocytes migrate through the pores of filter towards the chemotactic agent**



POLLS 3

Scan or Click to watch Cell Adaptation & Injury

Scan or Click to watch Apoptosis & Necrosis

Scan or Click to watch Inflammation

Scan or Click to watch Haemodynamic Disorder

Correct sequence in extravasation of leukocytes is -

- a) Margination - rolling- adhesion - transmigration
- b) Transmigration- margination - rolling- adhesion
- c) Rolling- adhesion- transmigration- margination
- d) Adhesion- transmigration- margination- rolling

Correct sequence in extravasation of leukocytes is -

- a) Margination - rolling- adhesion - transmigration
- b) Transmigration- margination - rolling- adhesion
- c) Rolling- adhesion- transmigration- margination
- d) Adhesion- transmigration- margination- rolling

Leukocyte migration through capillary wall is called?

- a) Rolling
- b) Diapedesis
- c) Migration
- d) Pavementing

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- a) Rolling
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Rolling of leucocytes on endothelial cells is mediated by –

- a) ICAM-1
- b) B2 integrin
- c) IL-8
- d) P- selectin

Rolling of leucocytes on endothelial cells is mediated by –

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PECAM-1 (CD-31) **PECAM-1 (CD-31 [AI 15])** **Diapedesis [AIIMS 14] (transmigration)**

Most important for diapedesis ?

- a) PECAM
- b) Selectin
- c) Integrin
- d) Mucin like glycoprotein

Most important for diapedesis ?

- a) PECAM
- b) Selectin
- c) Integrin
- d) Mucin like glycoprotein

All of Which is family of selectin, except -

- a) P selectin
- b) L selectin
- c) A selectin
- d) E selectin

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All of Which is family of selectin, except -

- a) P selectin
- b) L selectin
- c) A selectin
- d) E selectin

The most important meditor of chemotaxis among following is -

- a) C3b
- b) C5a
- c) C567
- d) C2

The most important meditor of chemotaxis among following is -

- a) C3b
- b) C5a
- c) C567
- d) C2

Diapedesis primarily occurs in?

a) Arterioles
b) Venules
c) Capillaries
d) None

B

Earliest transient change following tissue injury will be -

a) Neutropenia
b) Neutrophilia
c) Monocytosis
d) Lymphocytosis

B

Chemotaxis in response to activation of cells results in -

a) Random multidirectional movement
b) Unidirectional motion
c) Adhesion to endothelium
d) Augmeted oxygen dependent bactericidal effect

B

Chemotaxis is mediated by-

a) Histamine
b) Leukotriene B4 and C5a
c) Leukotriene C4 and C3a
d) Bradykinin

B

Immediate transient type of increase vascular permeability in acute inflammation -

a) Venules
b) Capillaries
c) Arterioles
d) None

A

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In acute inflammation endothelial retraction leads to:

(a) Delayed transient increase in permeability
(b) Immediate transient increase in permeability
(c) Delayed prolonged increase in permeability
(d) Immediate transient decrease in permeability

c

Delayed prolonged bleeding is caused by:

(a) Histamine

(b) Endothelial retraction

(c) IL-1

(d) Direct injury to endothelial cells

D

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Diapedesis is:

(a) Immigration of leukocytes through the basement membrane

(b) Immigration of the leukocytes through the vessel wall to the site of inflammation

(c) Aggregation of platelets at the site of bleeding

(d) Auto digestion of the cells

B

Cellular events

1. Margination and pavementing
2. Rolling
3. Adhesion
4. Transmigration (diapedes)
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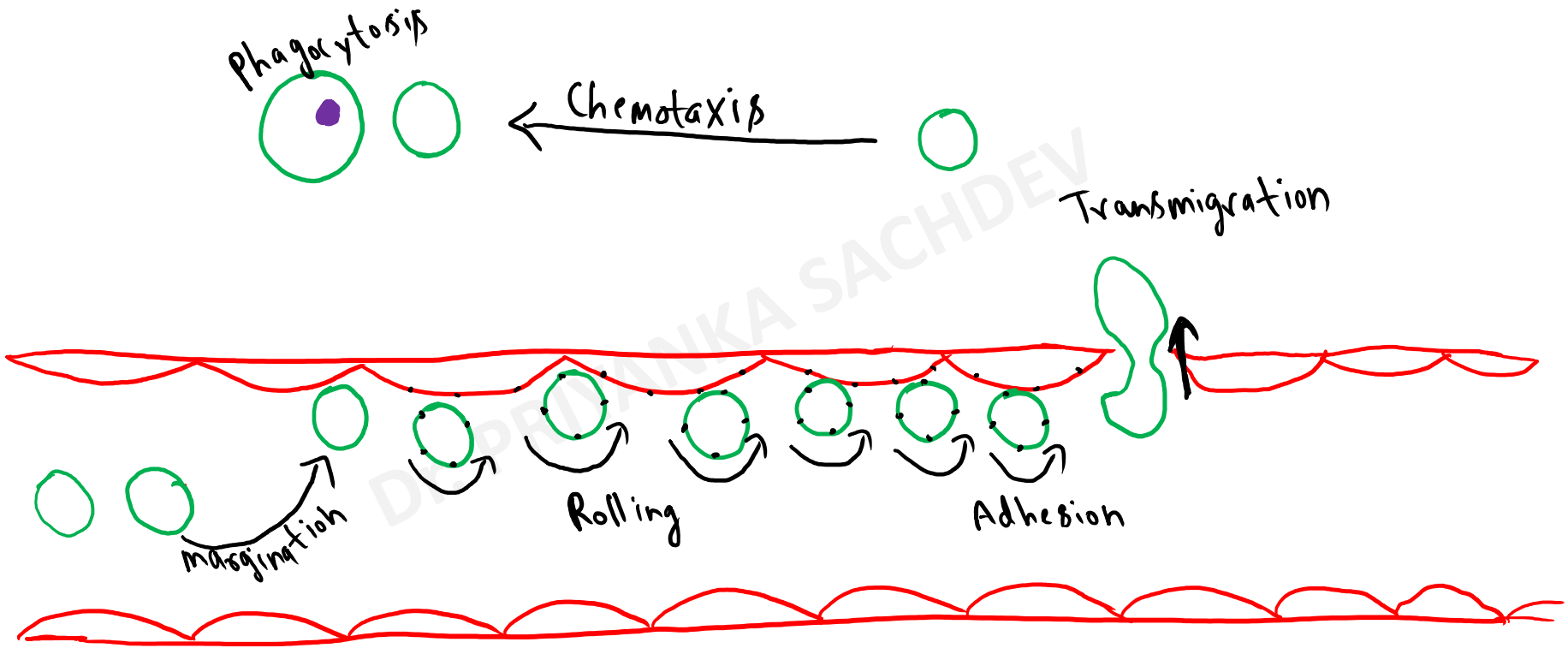
Phagocytosis

The process of **engulfment of microbes by the WBC's (cell-eating)**

- Cells performing this function are called **phagocytes**



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- There are 2 types of phagocytic cells:

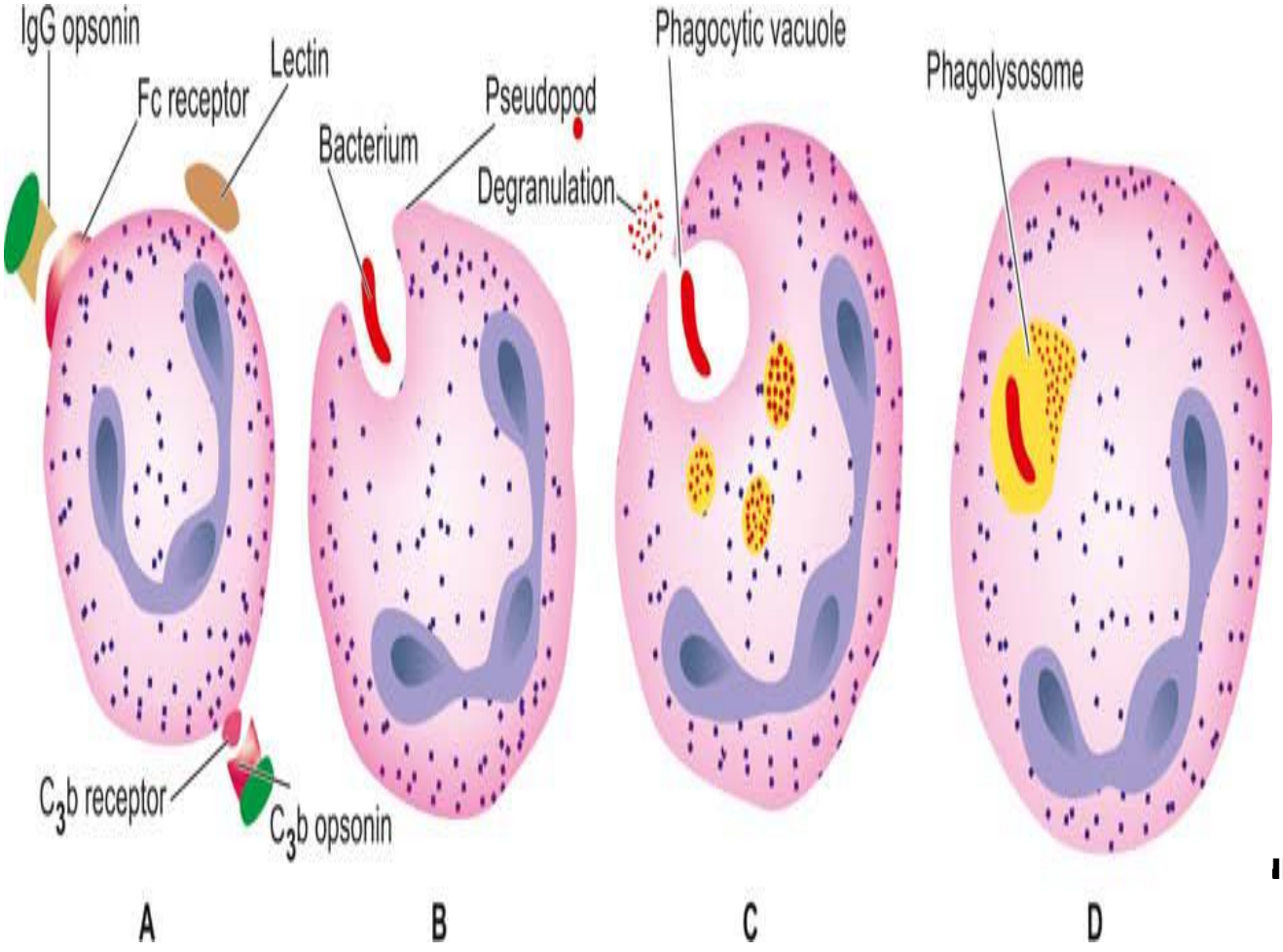
1) Polymorphonuclear neutrophils (PMNs) which appear early in acute inflammatory response

2) Monocytes commonly called as macrophages

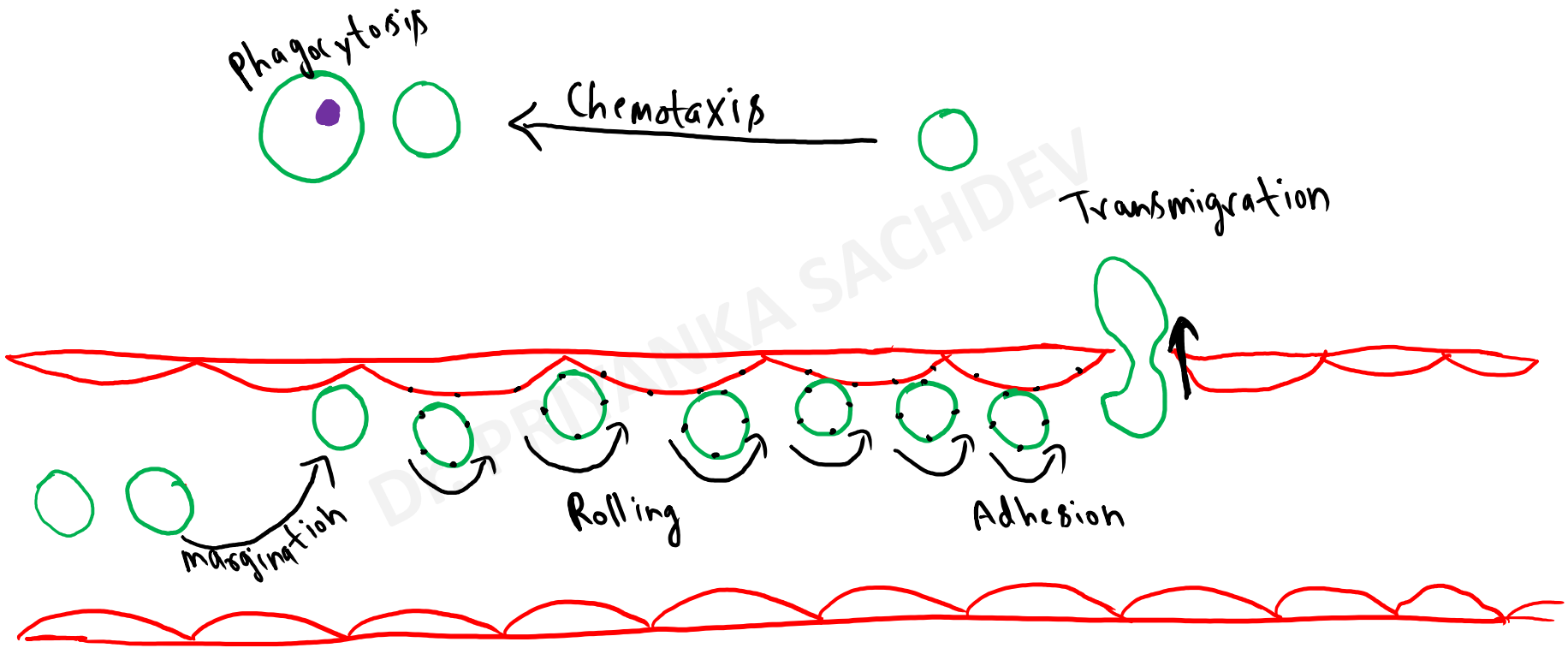
Phagocytsis

This sequence was appreciated by **Metchnikoff (1880)**

1. **Recognition and Attachement**
2. **Engulfment**
3. **Killing and degradation**


IgG opsonin
Fc receptor
Lectin
Bacterium
Pseudopod
Degranulation
Phagocytic vacuole
Phagolysosome
C3b receptor
C3b opsonin
A
B
C
D

IKA SACHDEV



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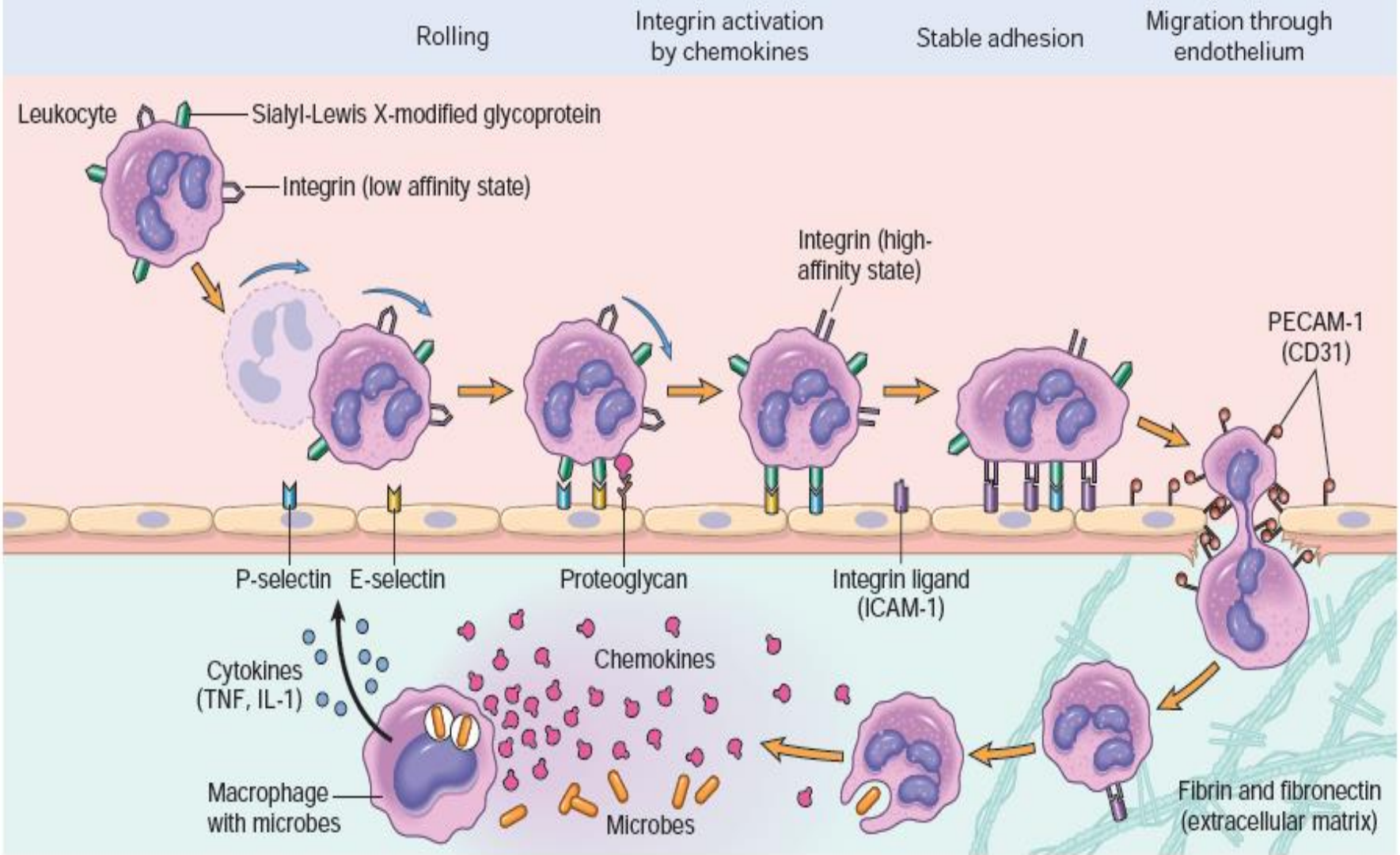
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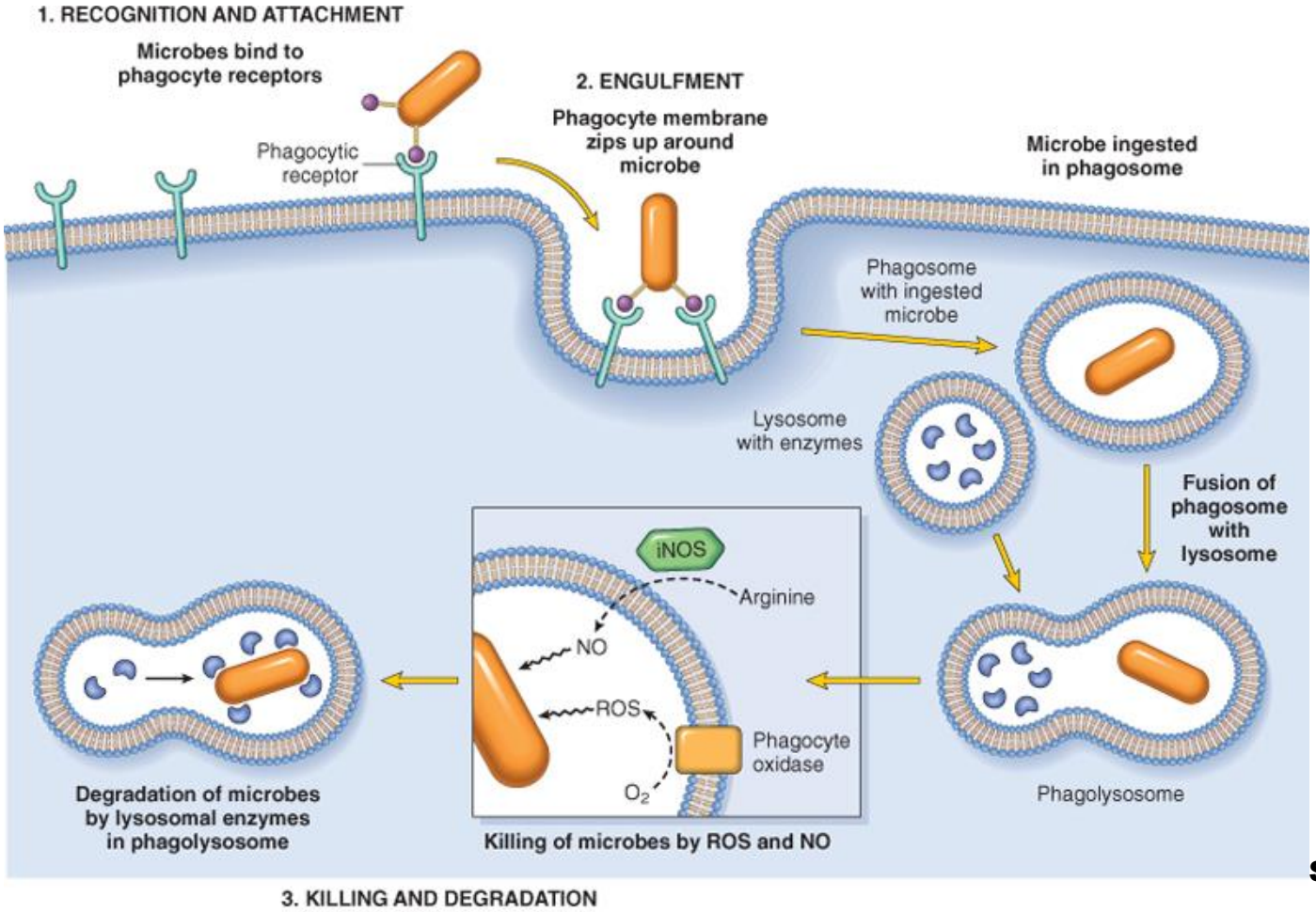
1. RECOGNITION AND ATTACHMENT
Microbes bind to phagocyte receptors
Phagocytic receptor
2. ENGULFMENT
Phagocyte membrane zips up around microbe
Microbe ingested in phagosome
Phagosome with ingested microbe
Lysosome with enzymes
Fusion of phagosome with lysosome
iNOS
Arginine
NO
ROS
Phagocyte oxidase
O_2
Phagolysosome
Degradation of microbes by lysosomal enzymes in phagolysosome
Killing of microbes by ROS and NO
3. KILLING AND DEGRADATION

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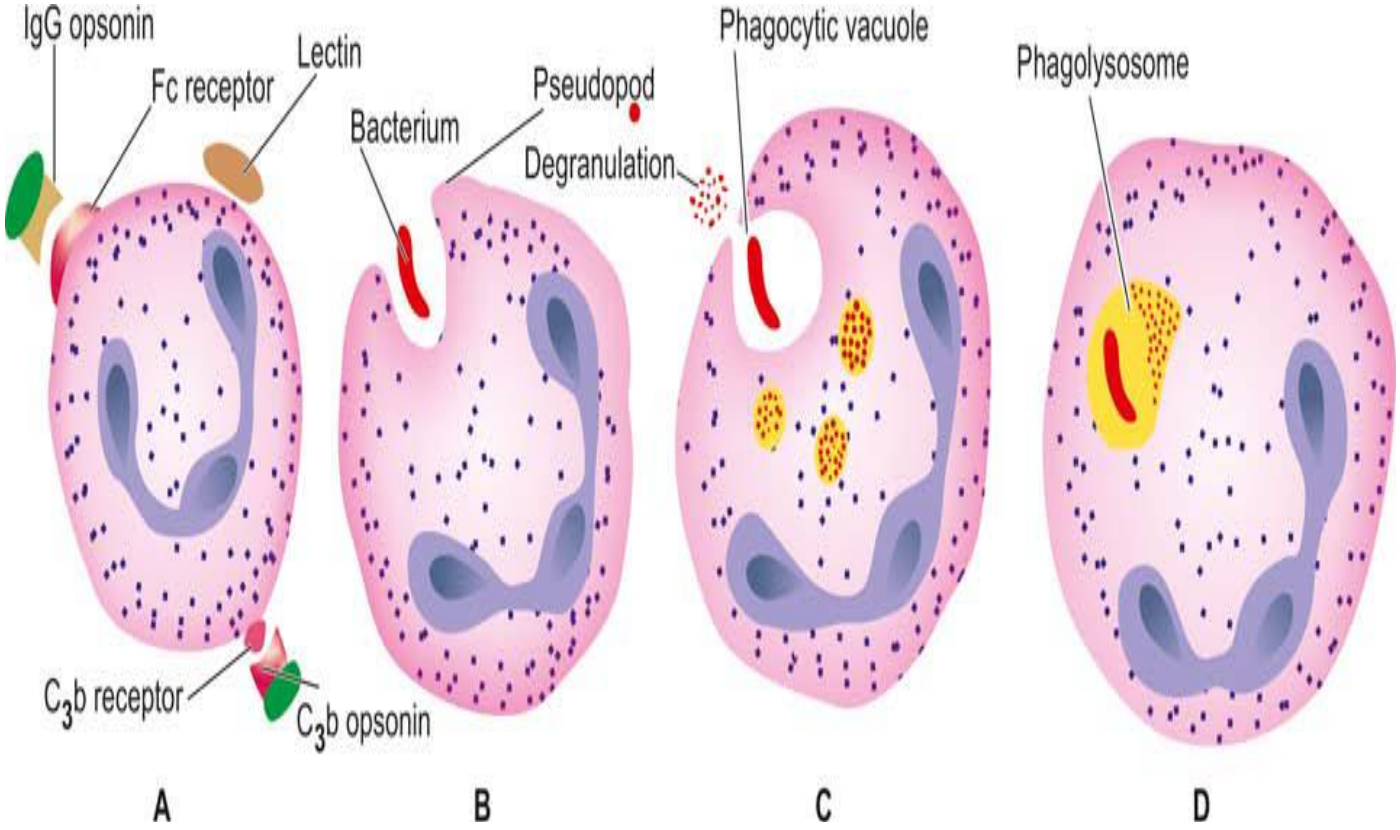
1.Recognition and Attachement

- **Receptors on surface of macrophages→**

1. Mannose receptor
2. Scavenger receptor
3. Receptors for opsonin
4. Macrophage intergrins (Mac1)(CD11b/CD18)



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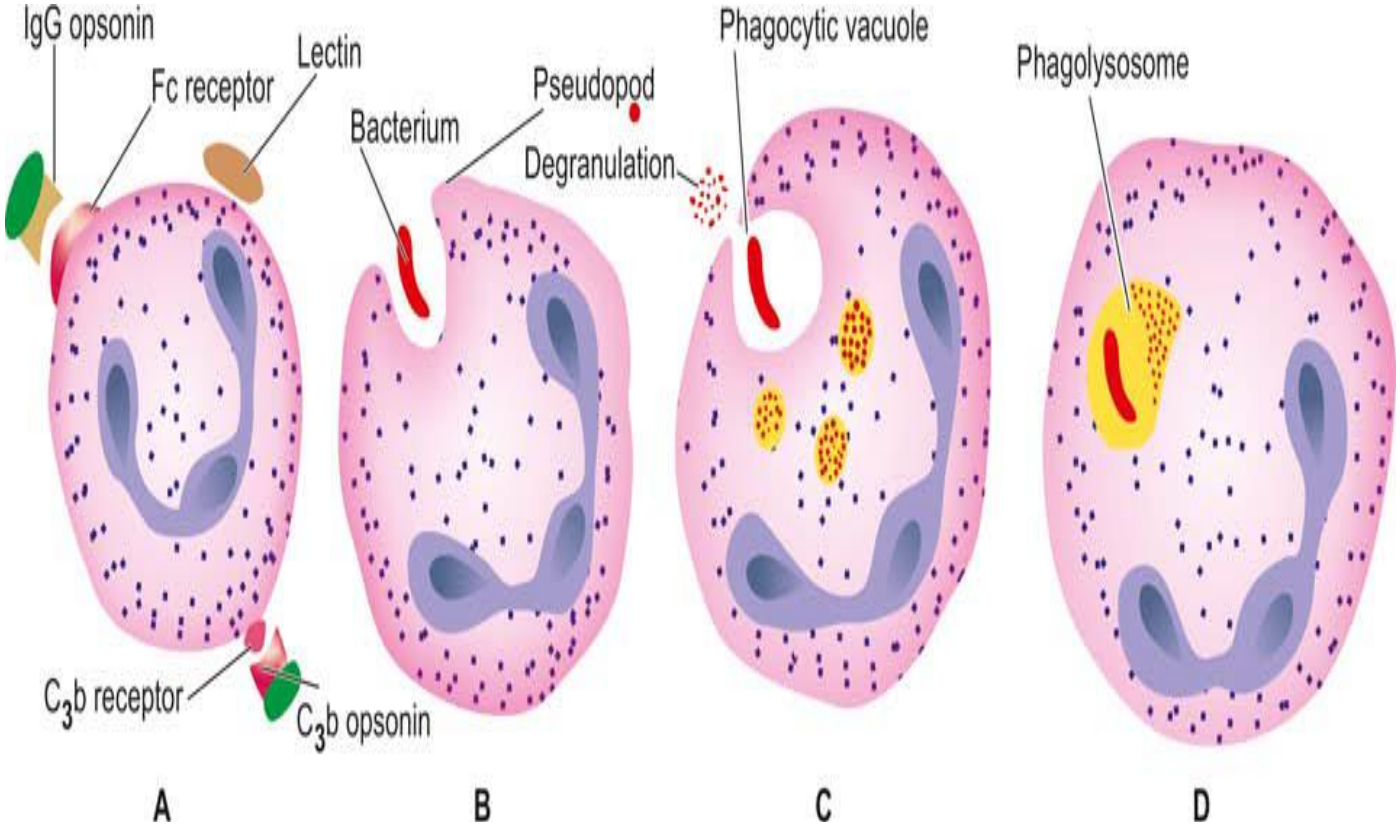
Engulfment

- Activation of **actin filaments**
- Formation of **cytoplasmic pseudopods around the particle**
- **Enveloping it**
- Formation of **phagocytic vacuole**
- **plasma membrane enclosing the particle breaks** from the cell surface
- membrane-lined phagosome becomes **internalised** in the cell
- The phagosome fuses with one or more lysosomes of the cell and form bigger vacuole called **phagolysosome**



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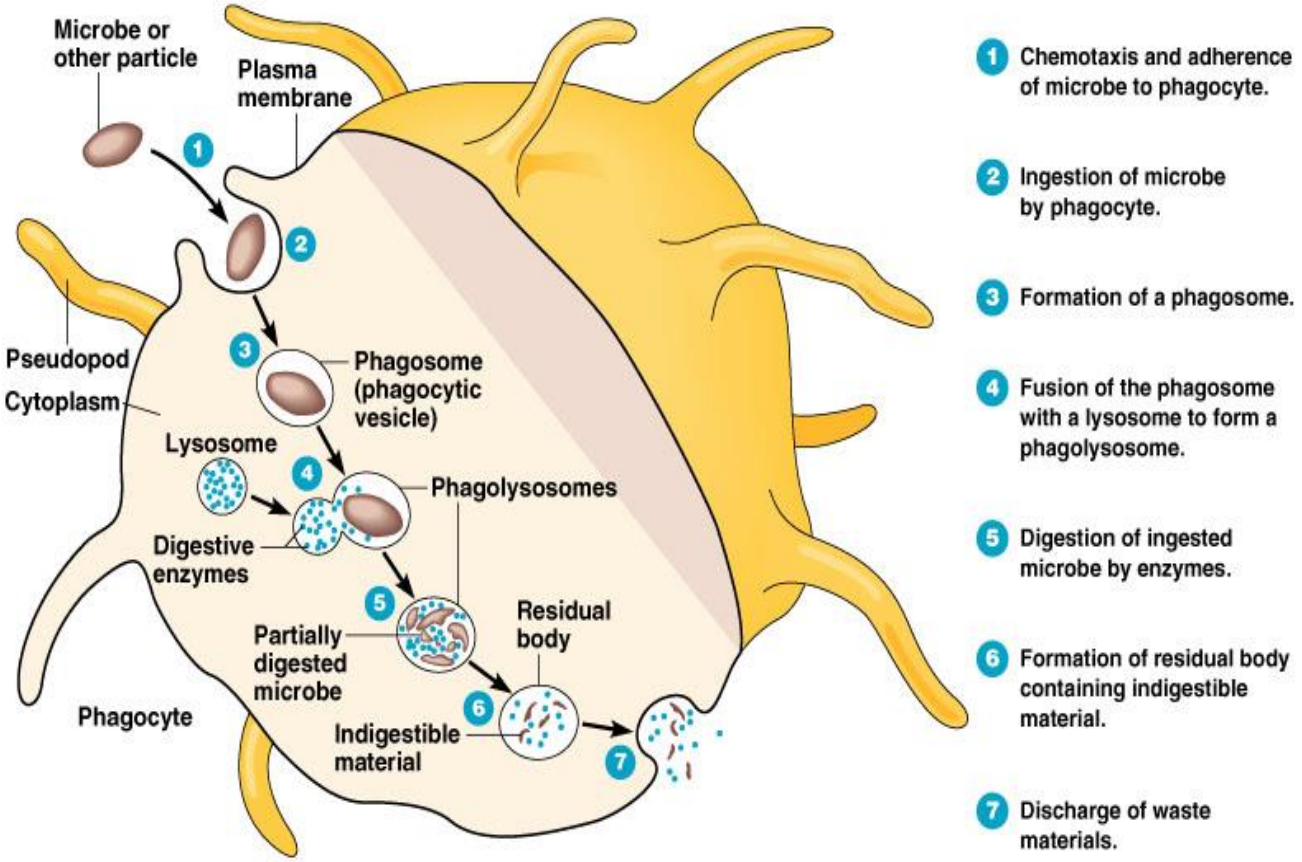
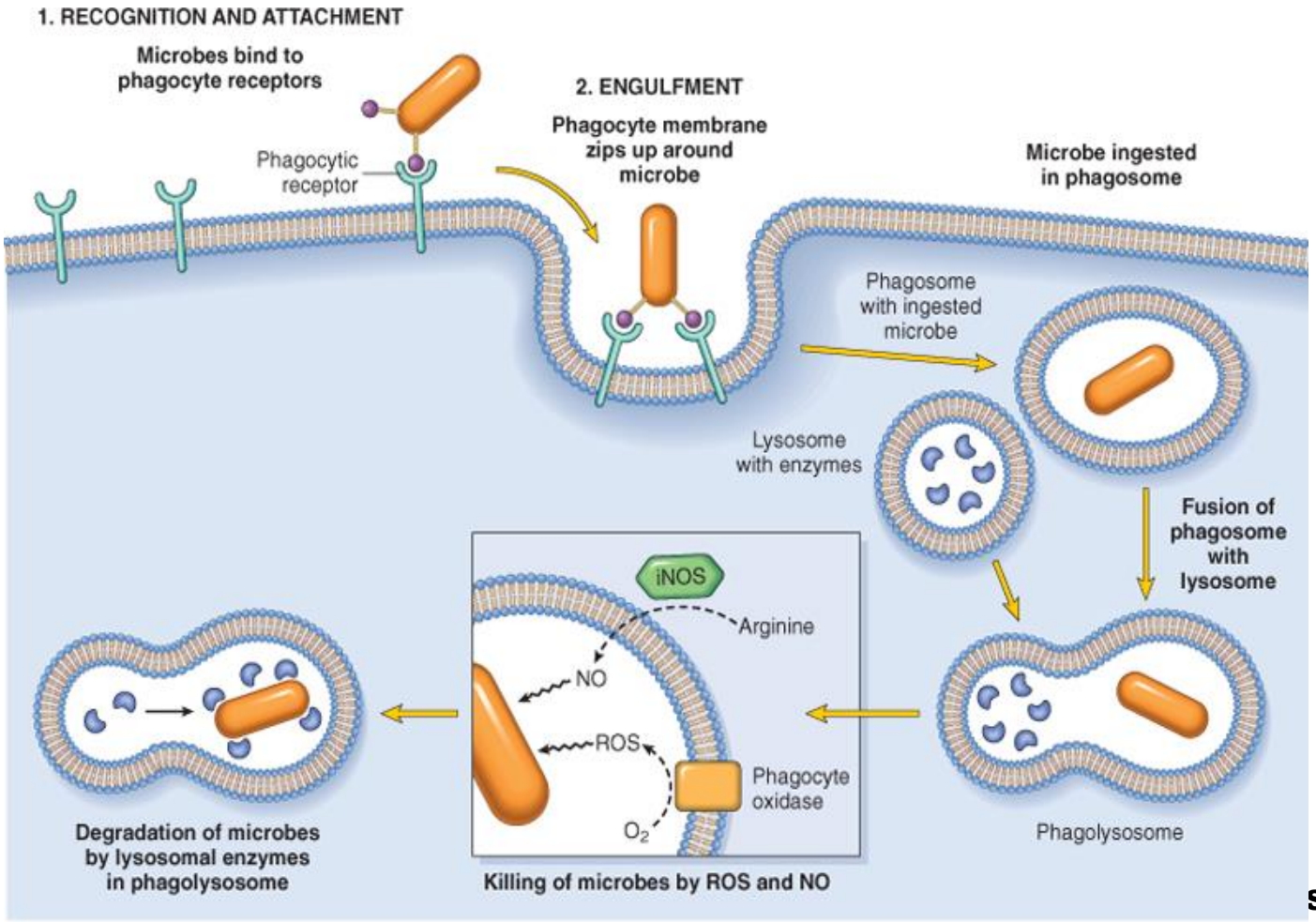


(a) Phases of phagocytosis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Fusion of phagosome with lysosome
iNOS
Arginine
NO
ROS
Phagocyte oxidase
O_2
Phagolysosome
Degradation of microbes by lysosomal enzymes in phagolysosome
Killing of microbes by ROS and NO
3. KILLING AND DEGRADATION

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Killing and degradation

i) Oxidative bactericidal mechanism by **oxygen free radicals**

- a) MPO-dependent
- b) MPO-independent

ii) Oxidative bactericidal mechanism by **lysosomal granules**

iii) **Non-oxidative bactericidal mechanism**

i) Oxidative bactericidal mechanism by oxygen free radicals

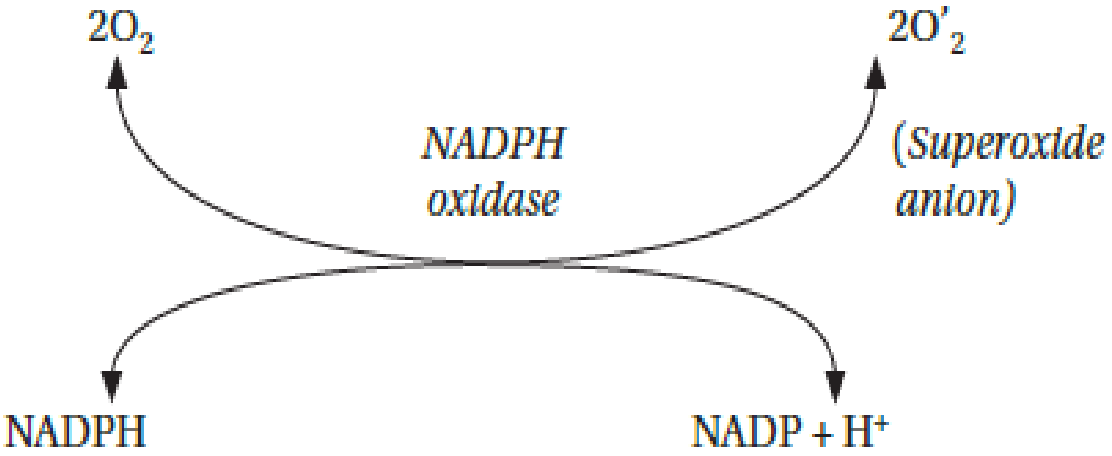
- By oxidative damage by the production of **reactive oxygen metabolites**

- **(O_2^- , H_2O_2 , OH^- , HOCl, HOI, HOBr)**

3 Steps

Step 1

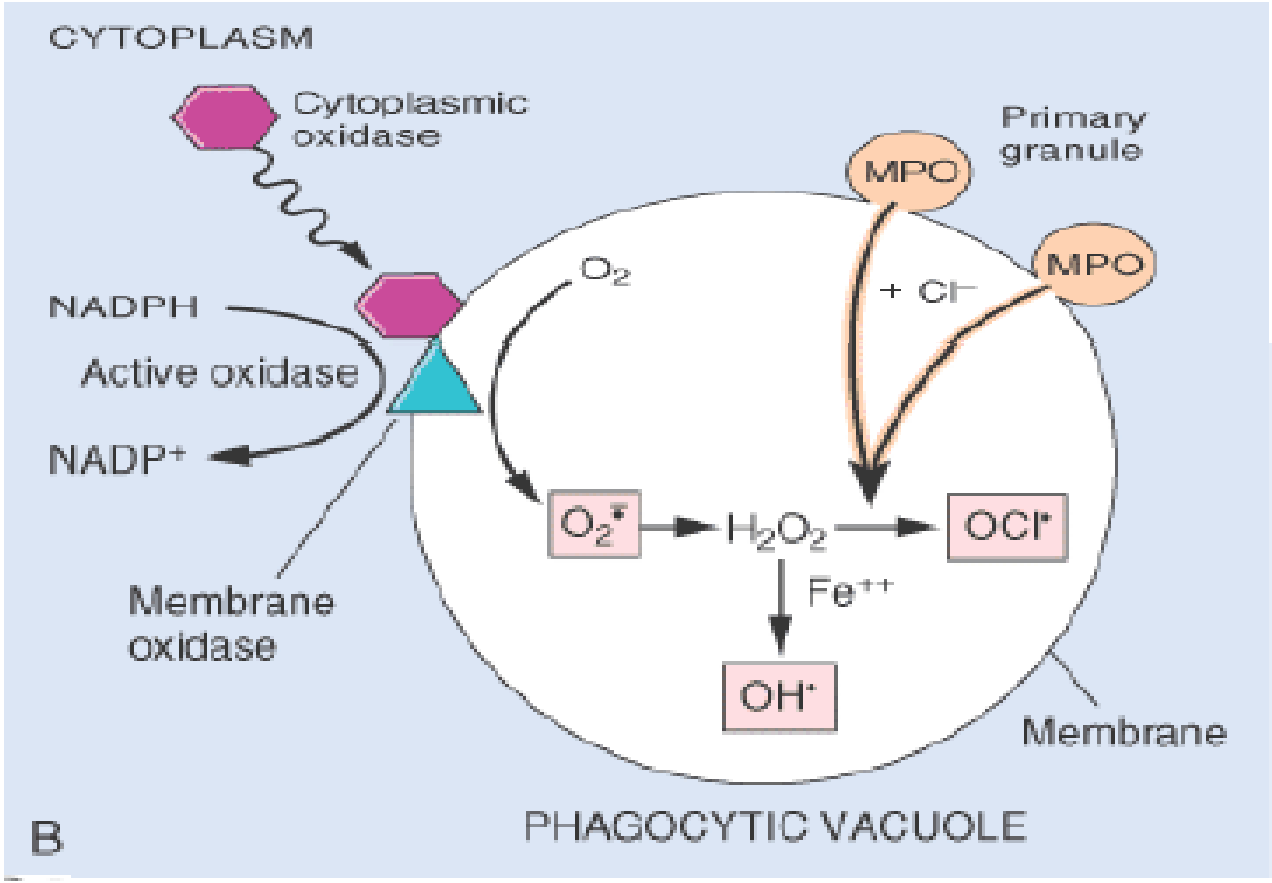
- NADPH-oxidase present in the cell membrane of phagosome reduces oxygen to superoxide ion (O2-)
- O2 ⟶ O2-
- This is known as **respiratory burst**



Superoxide is subsequently converted into H_2O_2 which has bactericidal properties:

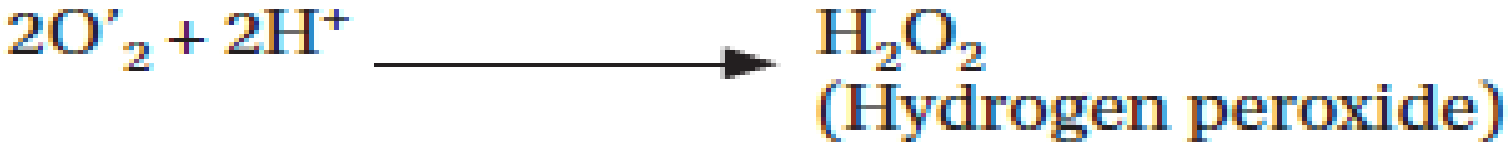
$$2O'_2 + 2H^+ \longrightarrow H_2O_2$$

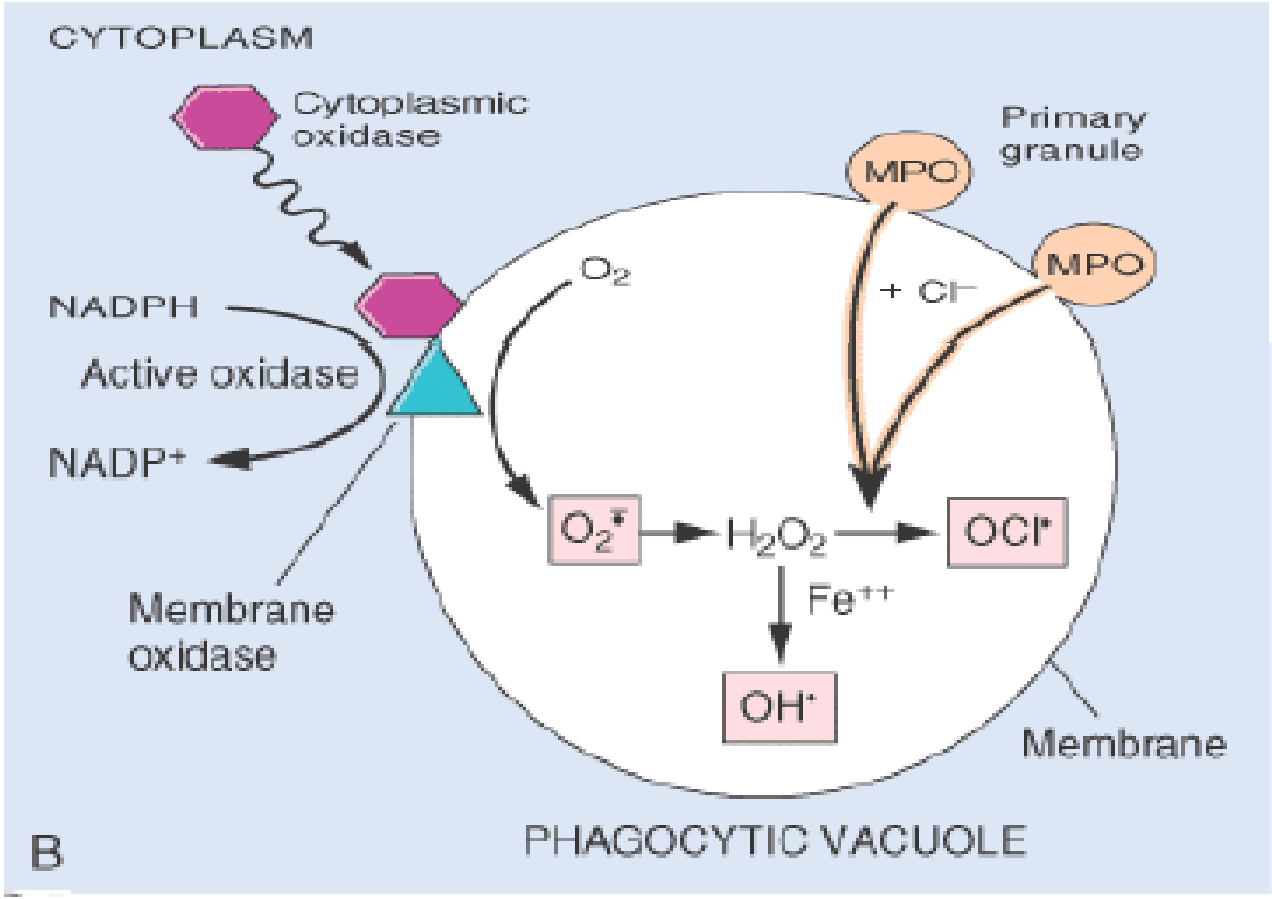
(Hydrogen peroxide)


CYTOPLASM
Cytoplasmic oxidase
NADPH
Active oxidase
NADP+
Membrane oxidase
Primary granule
MPO
MPO
O2
+ Cl−
O2•−
H2O2
OCl−
Fe++
OH•
Membrane
PHAGOCYTIC VACUOLE
B

Step 2

- Superoxide is subsequently converted into H2O2:





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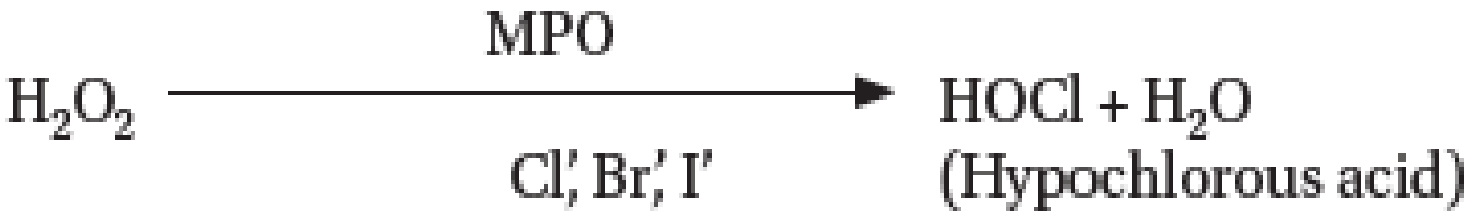
Step 3

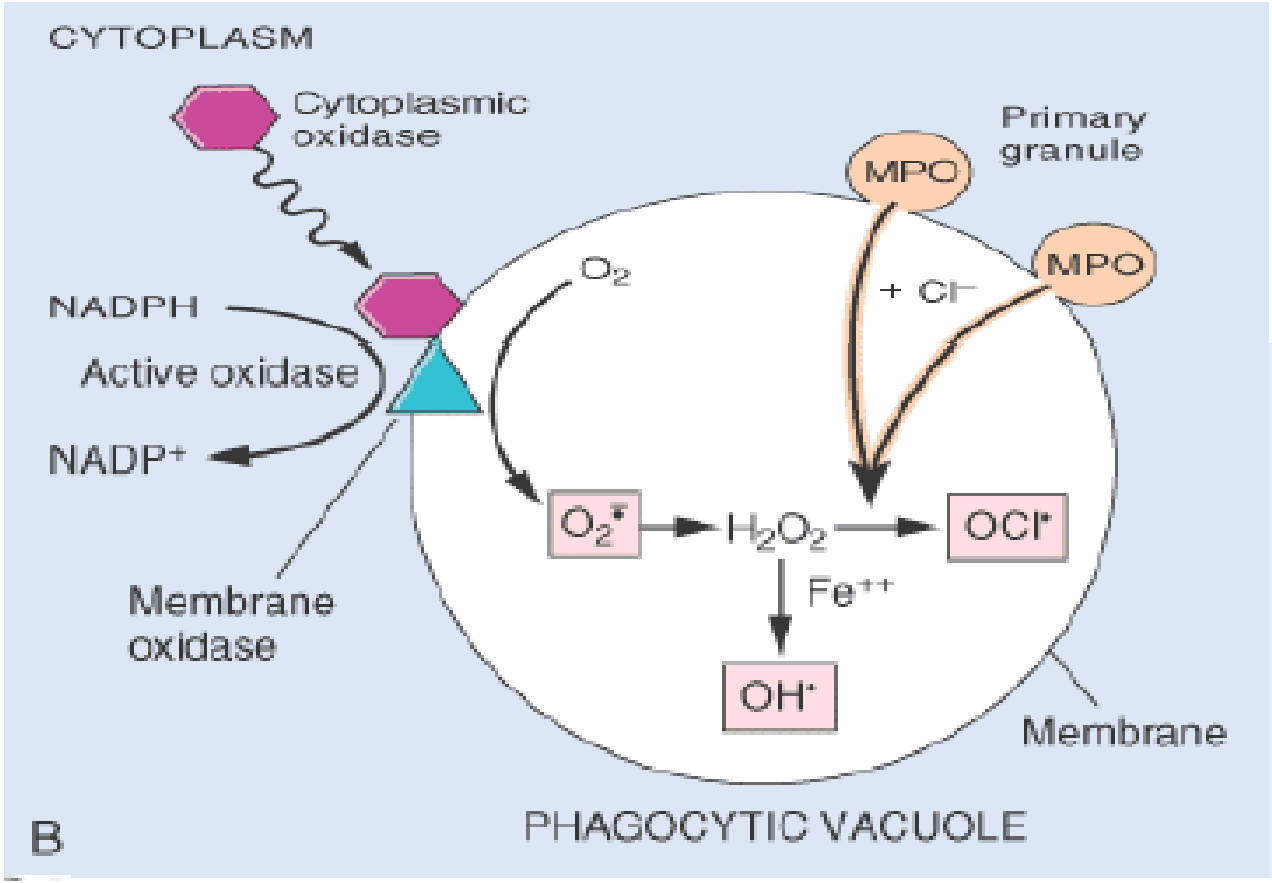
1. MPO-dependent killing
2. MPO-independent killing

MPO-dependent killing

- The enzyme MPO acts on H2O2 in the presence of halides (chloride, iodide or bromide) to form hypohalous acid (HOCl, HOI, HOBr).



- This is called **H2O2-MPO-halide system** and is more potent antibacterial system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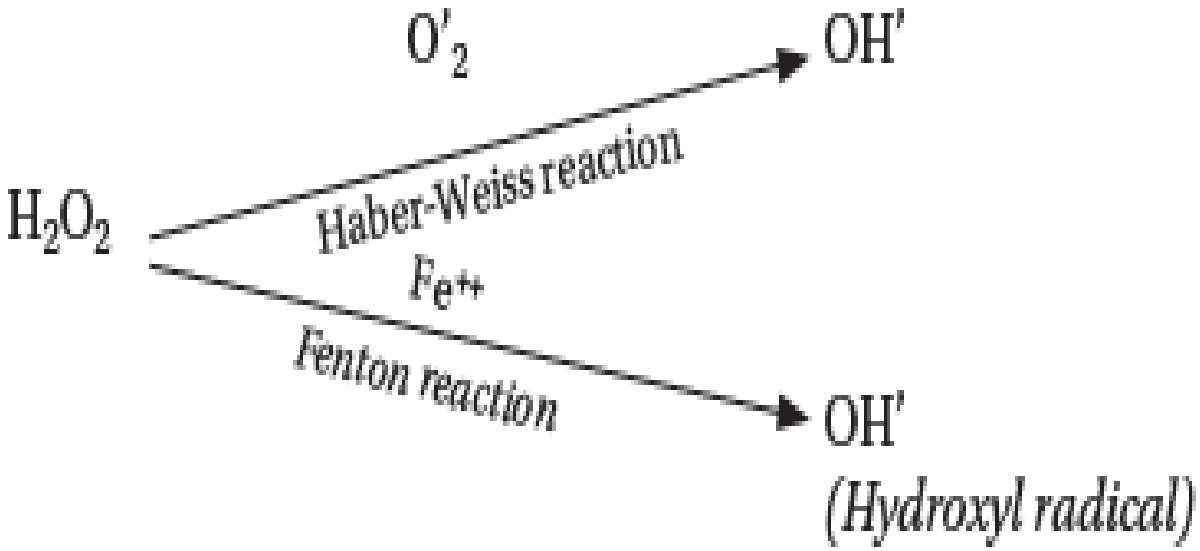
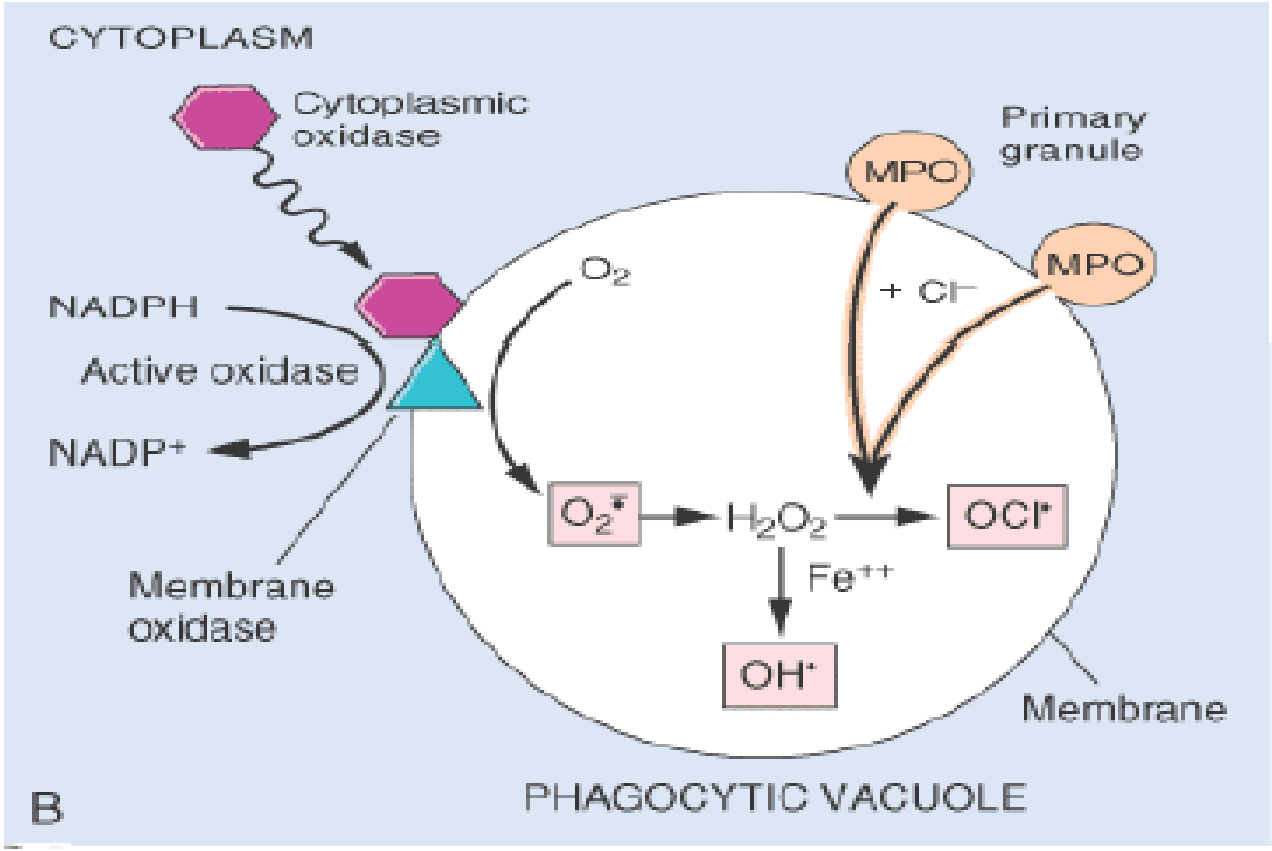
Cytoplasmic oxidase
NADPH
Active oxidase
NADP+
Membrane oxidase
Primary granule
MPO
MPO
O2
+ Cl−
O2•−
H2O2
OCl−
Fe++
OH•
Membrane
PHAGOCYTIC VACUOLE
B

MPO-independent killing

Mature macrophages lack the enzyme MPO and they carry out bactericidal activity by producing **OH–** ions from H2O2

- In the presence of O'2 **(Haber-Weiss reaction)**
- In the presence of Fe++ **(Fenton reaction)**


O'2
OH'
H2O2
Haber-Weiss reaction
Fe++
Fenton reaction
OH'
(Hydroxyl radical)


CYTOPLASM
Cytoplasmic oxidase
Primary granule
MPO
MPO
NADPH
Active oxidase
NADP+
O_2
+ Cl^-
$O_2^{\cdot-}$
H_2O_2
OCl^-
Fe^{++}
OH^-
Membrane oxidase
Membrane
B
PHAGOCYTIC VACUOLE

Killing and degradation

i) Oxidative bactericidal mechanism by **oxygen free radicals**

- a) MPO-dependent
- b) MPO-independent

ii) Oxidative bactericidal mechanism by **lysosomal granules**

iii) **Non-oxidative bactericidal mechanism**

ii) Oxidative bactericidal mechanism by lysosomal granules

- preformed granule-stored products of neutrophils and macrophages are discharged into the phagosome.

- **Protease, trypsinase, phospholipase, and alkaline phosphatase**

iii) Non-oxidative bactericidal mechanism

Nitric oxide

- Nitric oxide is a reactive free radicals similar to oxygen free radicals which is formed by nitric oxide synthase.

- It is produced by endothelial cells as well as by activated macrophages.

- Nitric oxide causes microbial killing.

POLLS 4

Scan or Click to watch Cell Adaptation & Injury

Scan or Click to watch Apoptosis & Necrosis

Scan or Click to watch Inflammation

Scan or Click to watch Haemodynamic Disorder

Phagocytosis was discovered by?

a) Elie Metchinkoff
b) Aulus Cornelius Celsus.
c) Rudolf Virchow
d) Emil Adolf von Behring

A

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Oxygen dependent killing is done through-

a) NADPH oxidase
b) Superoxide dismutase
c) Catalase
d) Glutathione peroxidase

A

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CHRONIC INFLAMMATION

DEFINITION

- Chronic inflammation is a response of prolonged duration (weeks or months) in which **inflammation, tissue injury and attempts at repair (fibrosis)** coexist, in varying combinations.

GENERAL FEATURES OF CHRONIC INFLAMMATION

- Inflammation (MONONUCLEAR CELL INFILTRATION)
- Tissue injury
- Attempts at repair (Fibrosis)

Blood monocytes

↓

on reaching the extravascular space

↓

Monocytes transform into tissue macrophage

↓

On activation

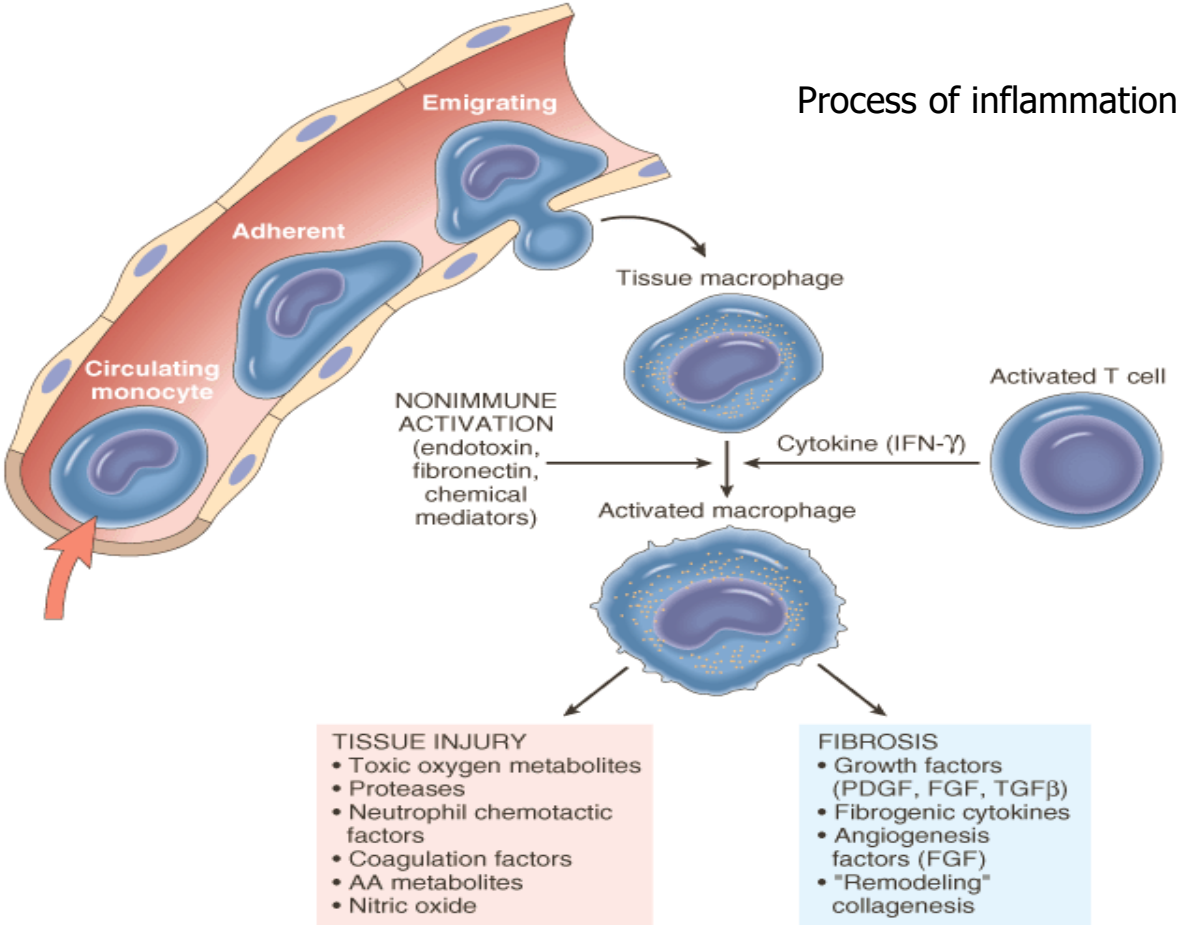
↓

macrophages release several biologically active substances

↓

These products bring about tissue destruction and fibrosis.

Process of inflammation



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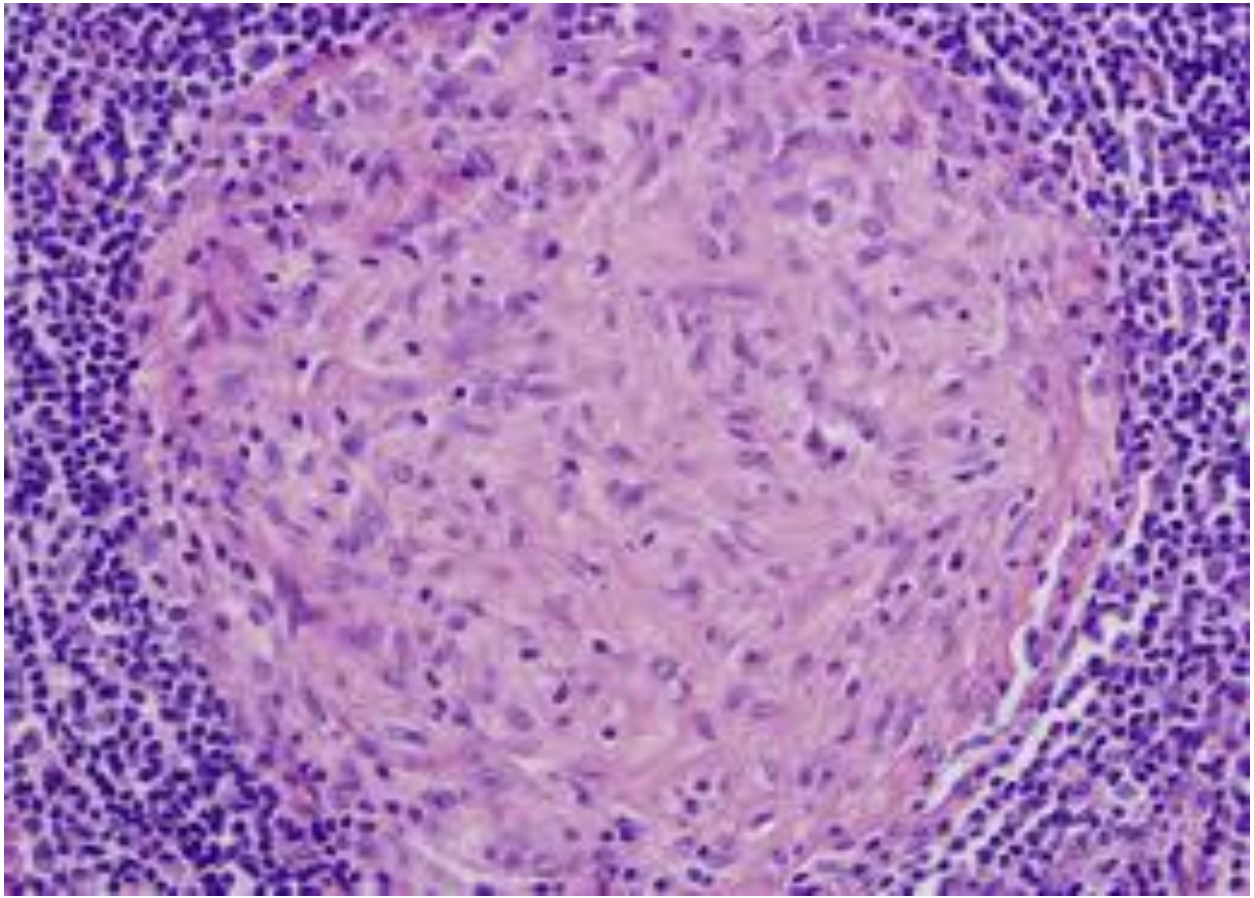
- Life span of monocytes in circulation is **1-3 days** whereas tissue macrophages have life span of **3 months to years**

GRANULOMATOUS INFLAMMATION

GRANULOMA →DEFINITION

- A granuloma is a **focus of chronic inflammation consisting of a microscopic aggregation of macrophages that are transformed into epithelium like cells (epithelioid cells)**
- Surrounded by a Collor of mononuclear leukocytes, principally **lymphocytes and plasma cells.**
- Frequently, these epitheloid cells fuse to form **giant cells**



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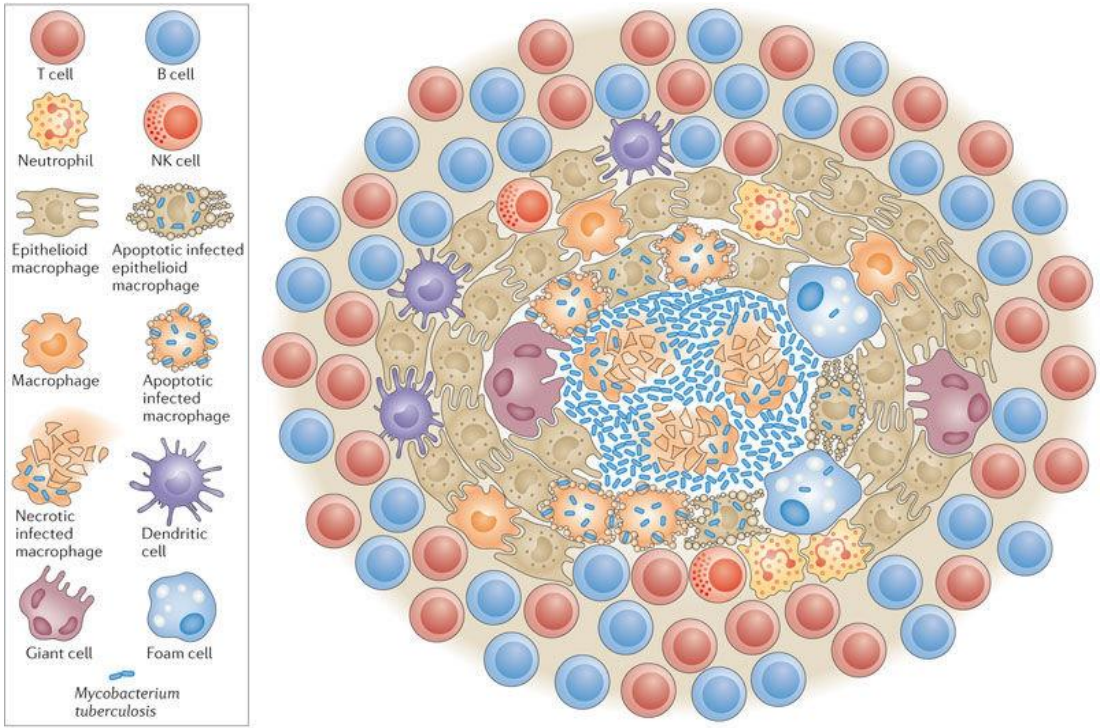

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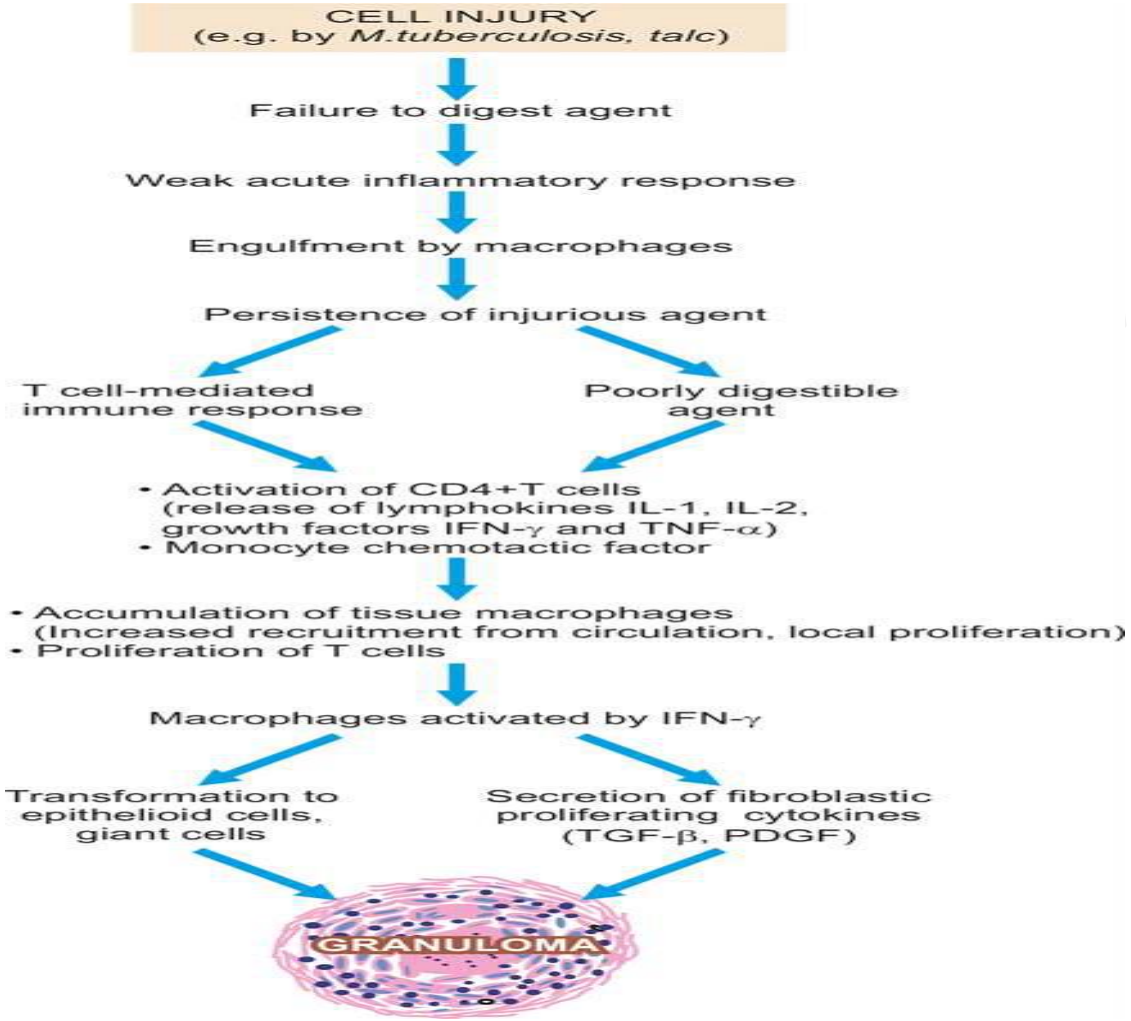
PATHOGENESIS OF GRANULOMA

- Formation of granuloma is a **type IV hypersensitivity reaction**
- It is a protective defense reaction by the host but eventually causes tissue destruction because of persistence of the **poorly digestible antigen**
- e.g. Mycobacterium tuberculosis, M. leprae,suture material, particles of talc etc



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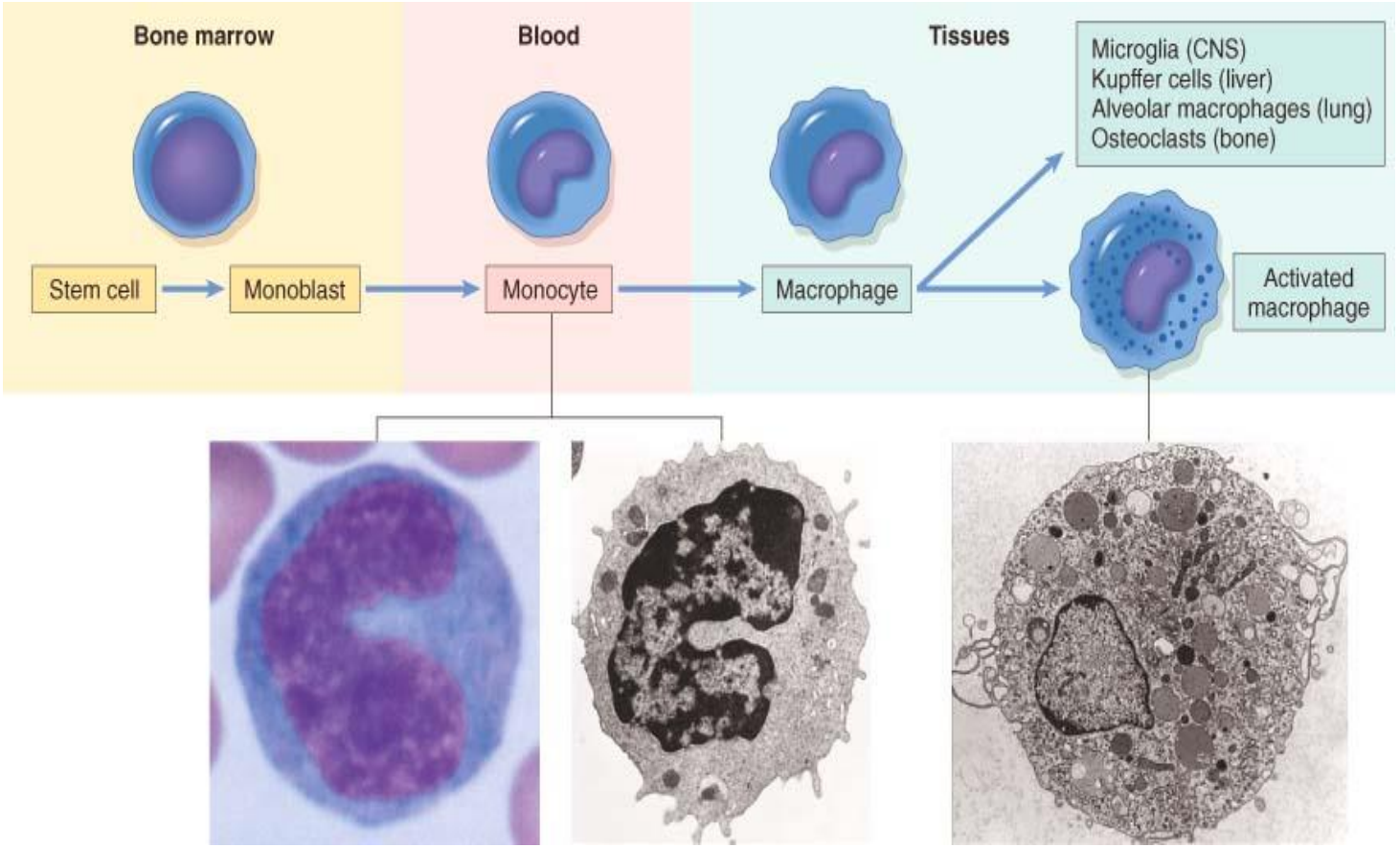

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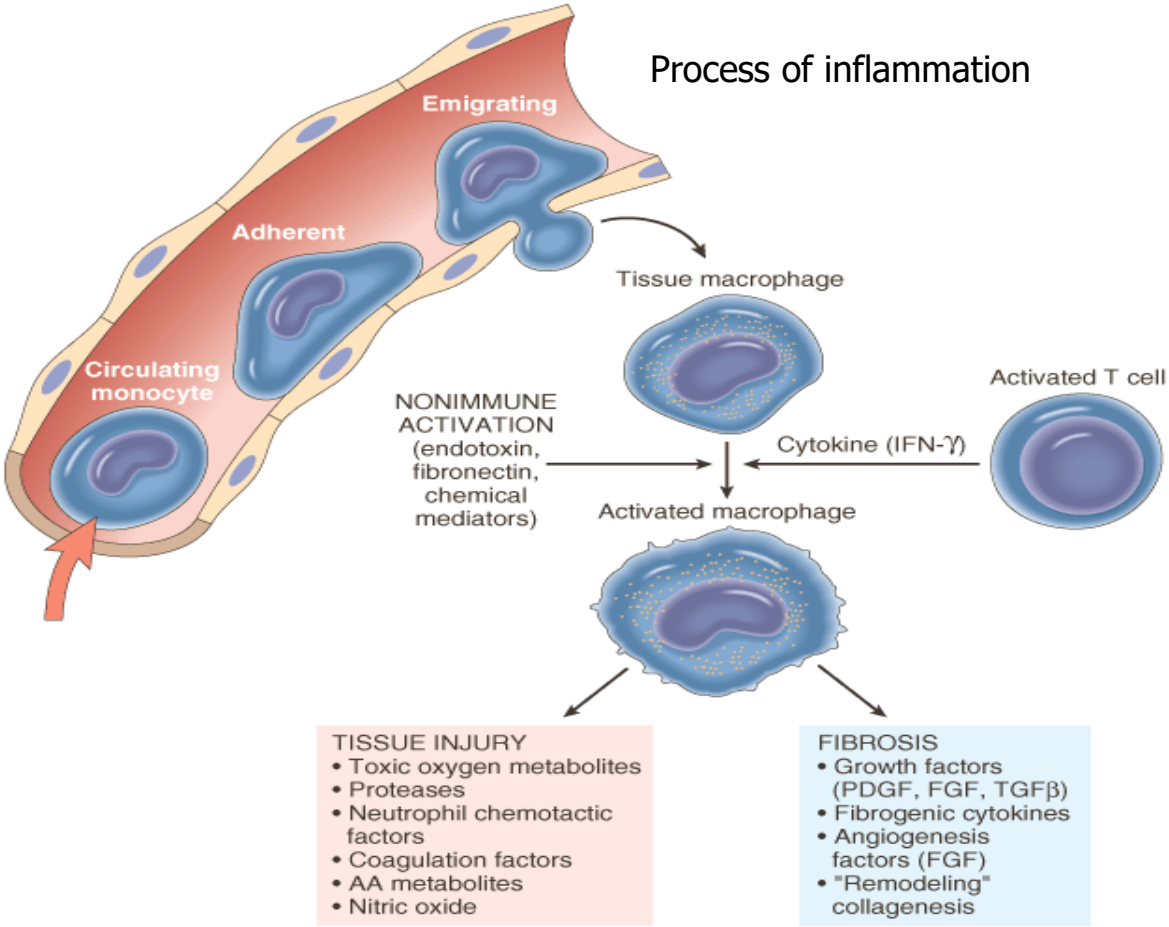
Process of inflammation



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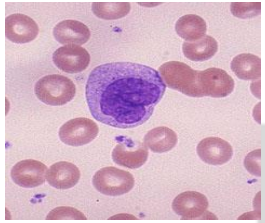
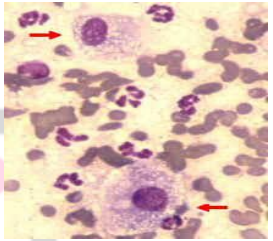
Monocyte



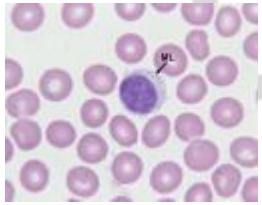
migrate into tissue within 48 hours

differentiate

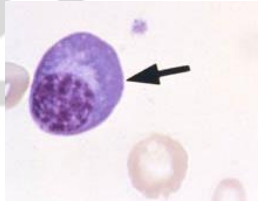
Macrophage



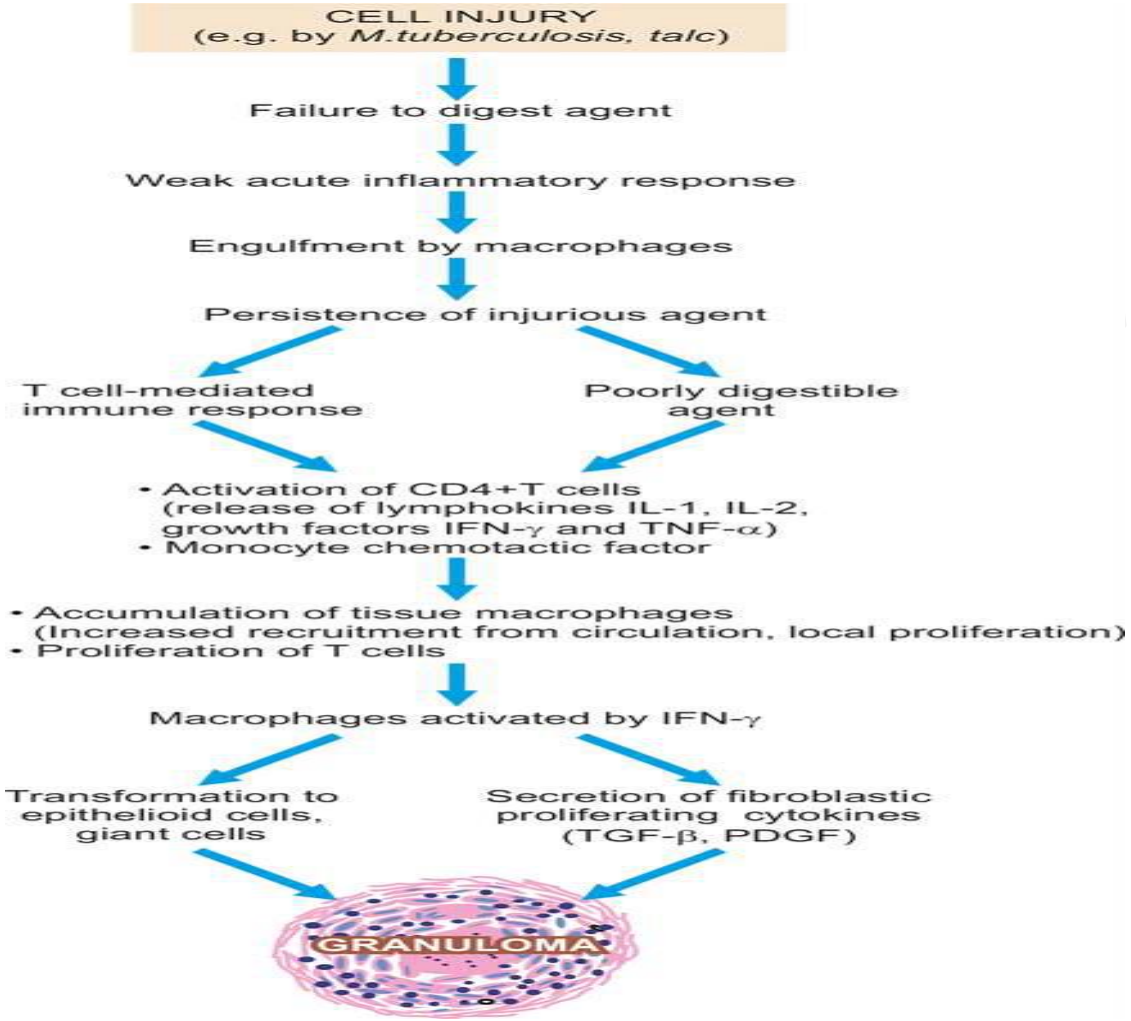
It is joined by lymphocytes and plasma cells, in chronic inflammation



Lymphocyte



Plasma cell



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- 1. Engulfment by macrophages
- 2.Activation of CD4+ T cells
- 3. Release of Cytokines

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1. Engulfment by macrophages

Macrophages engulf the antigen

↓

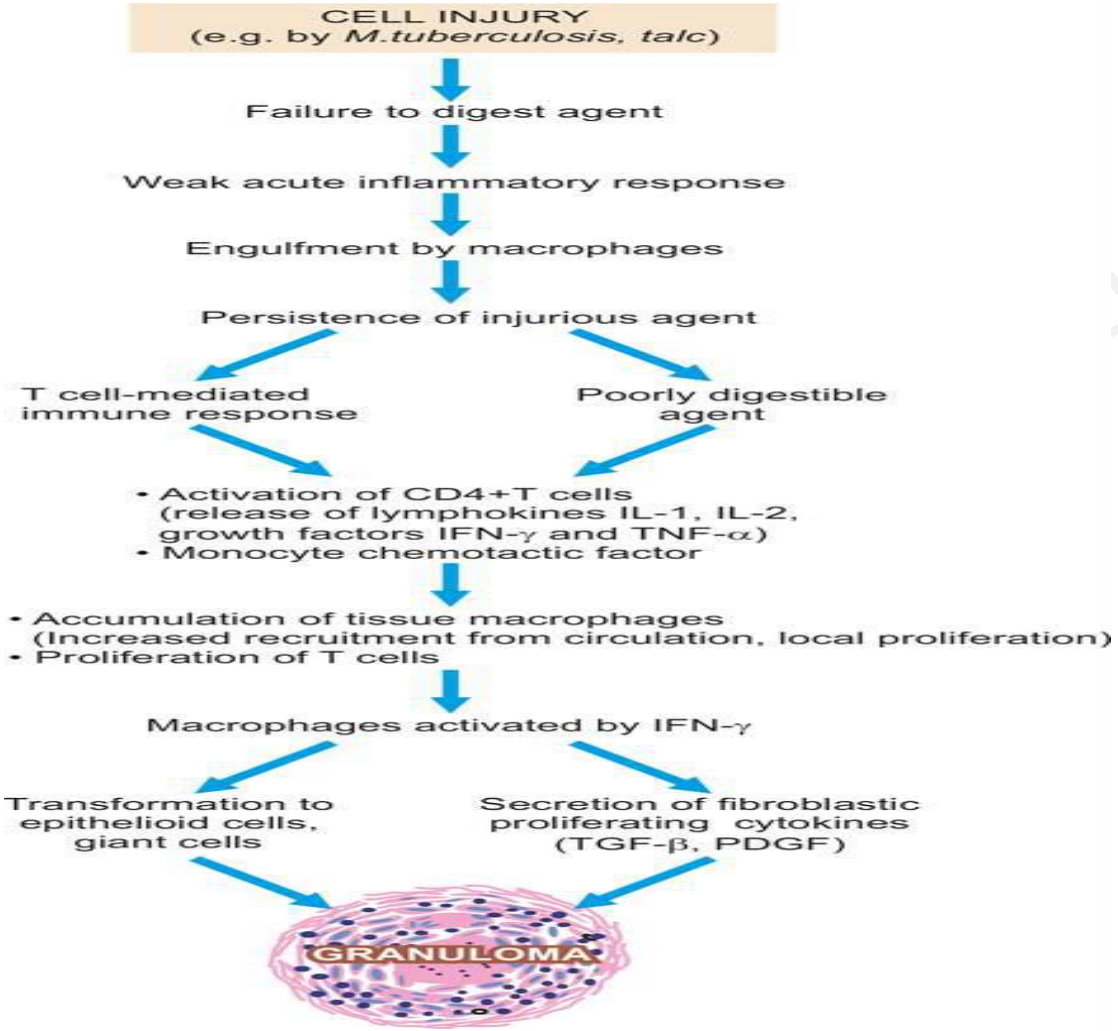
Try to destroy it

↓

But since the antigen is poorly degradable

↓

These cells fail to digest and degrade the antigen



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2.Activation of CD4+ T cells

Macrophages are antigen-presenting cells (APC)

↓

Having failed to deal with the antigen, they present antigen to CD4+ T lymphocytes

↓

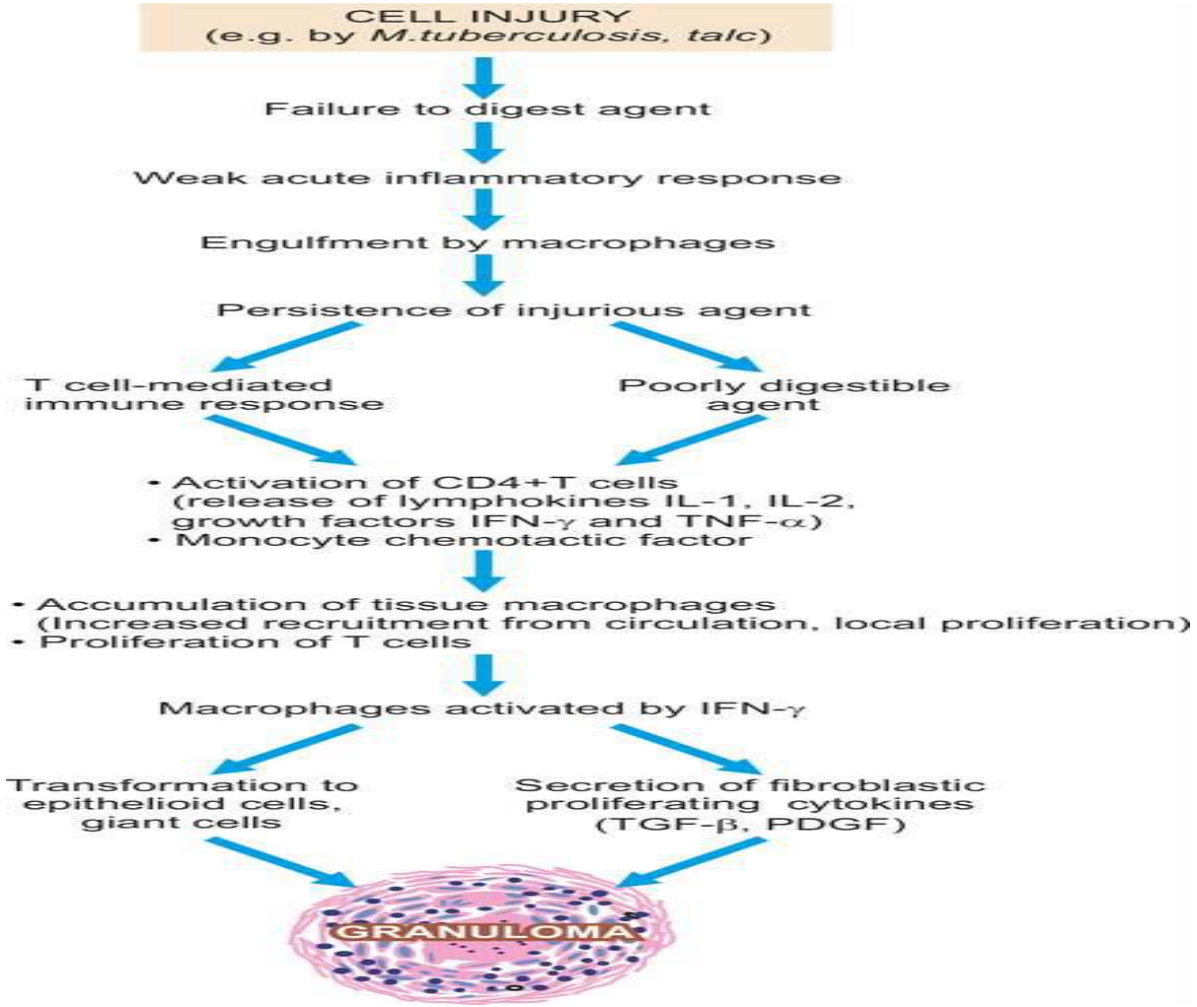
These lymphocytes get activated

↓

Release lymphokines

↓

IL-1, IL-2, interferon-Y, TNF-α



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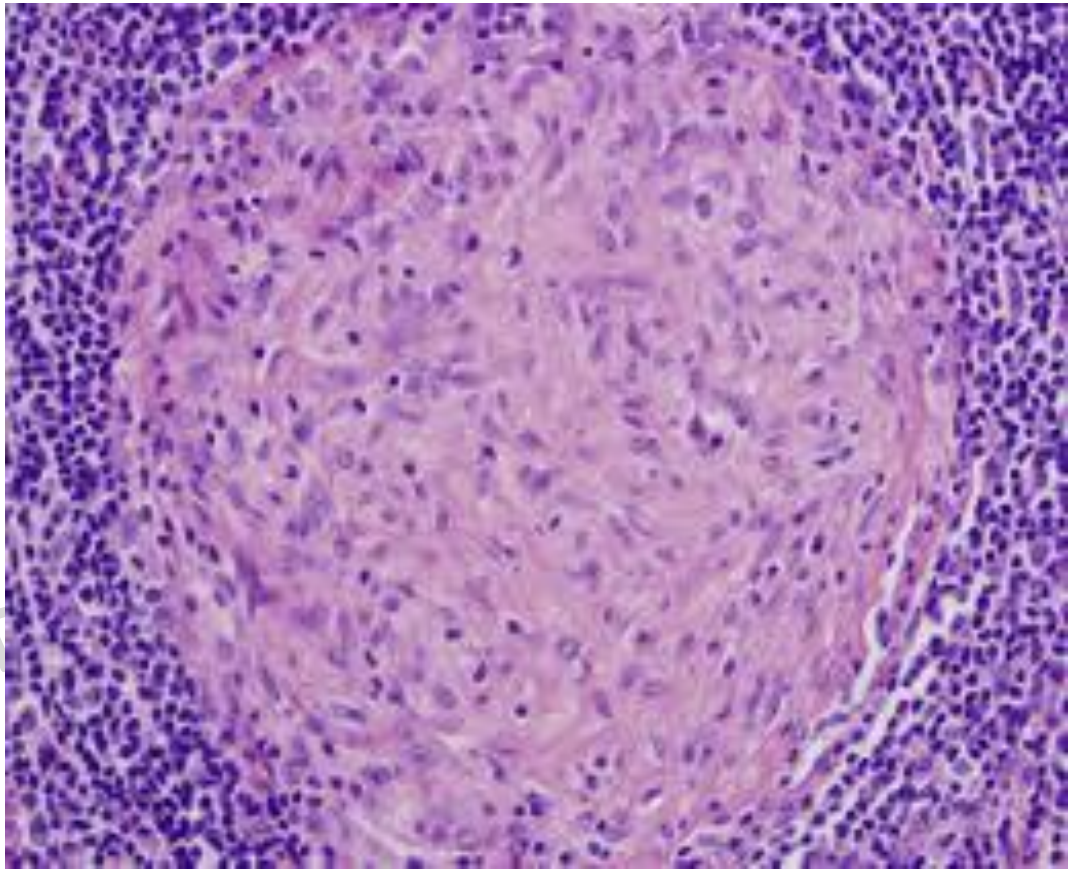
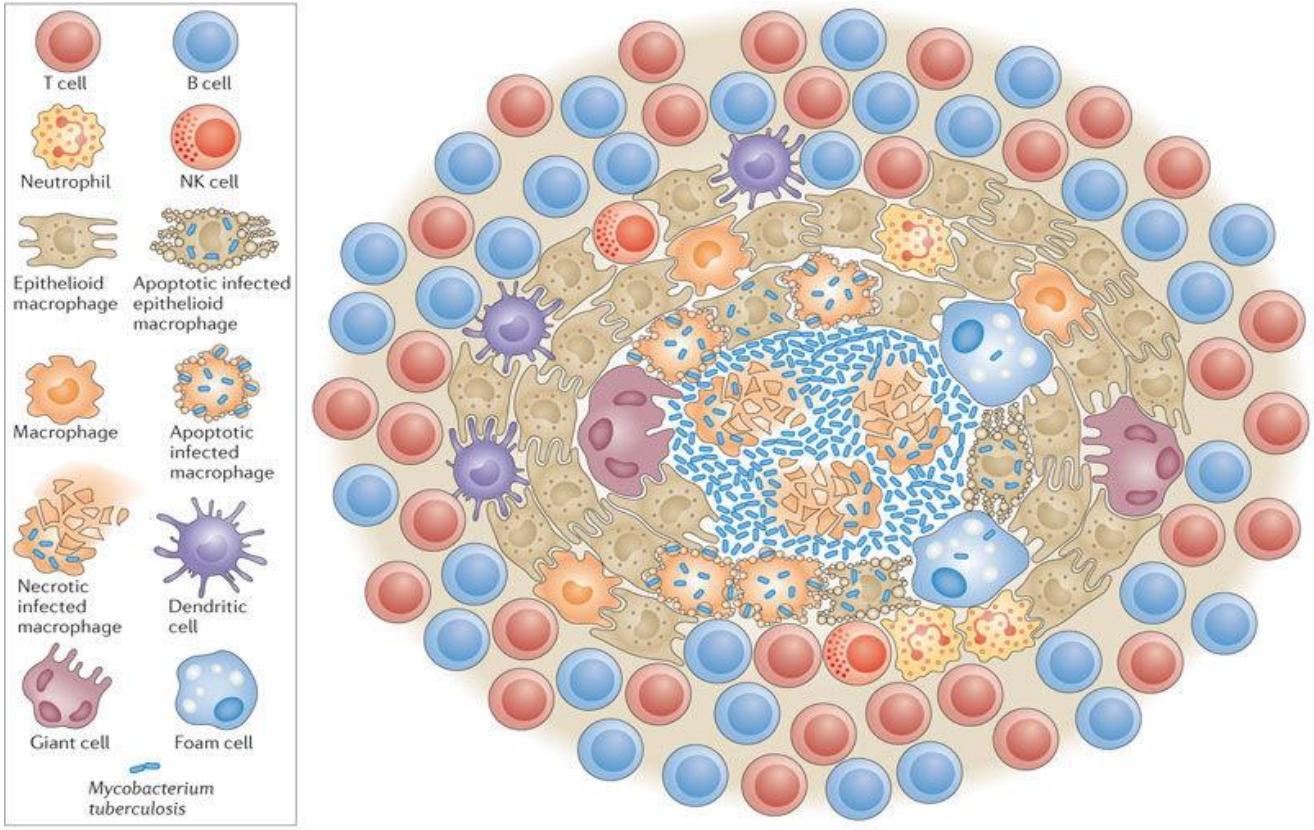
3. Release of Cytokines

- **i) IL-1 and IL-2** stimulate proliferation of more T cells.
- **ii) Interferon-γ** activates macrophages and transform it into epitheloid cells
- **iii) TNF-α** promotes fibroblast proliferation
- **iv) Growth factors (transforming growth factor-b, plateletderived growth factor)**

Thus, a granuloma is formed having

- Macrophages modified as epithelioid cells in the centre,
- Some epitheloid cells fuse to form multinucleate giant cells.
- Surrounded peripherally by lymphocytes (mainly T cells)
- Necrosis may be a feature of some granulomatous conditions
  - e.g. central caseation necrosis in tuberculosis (cheese-like)
- Healing by fibroblasts or collagen





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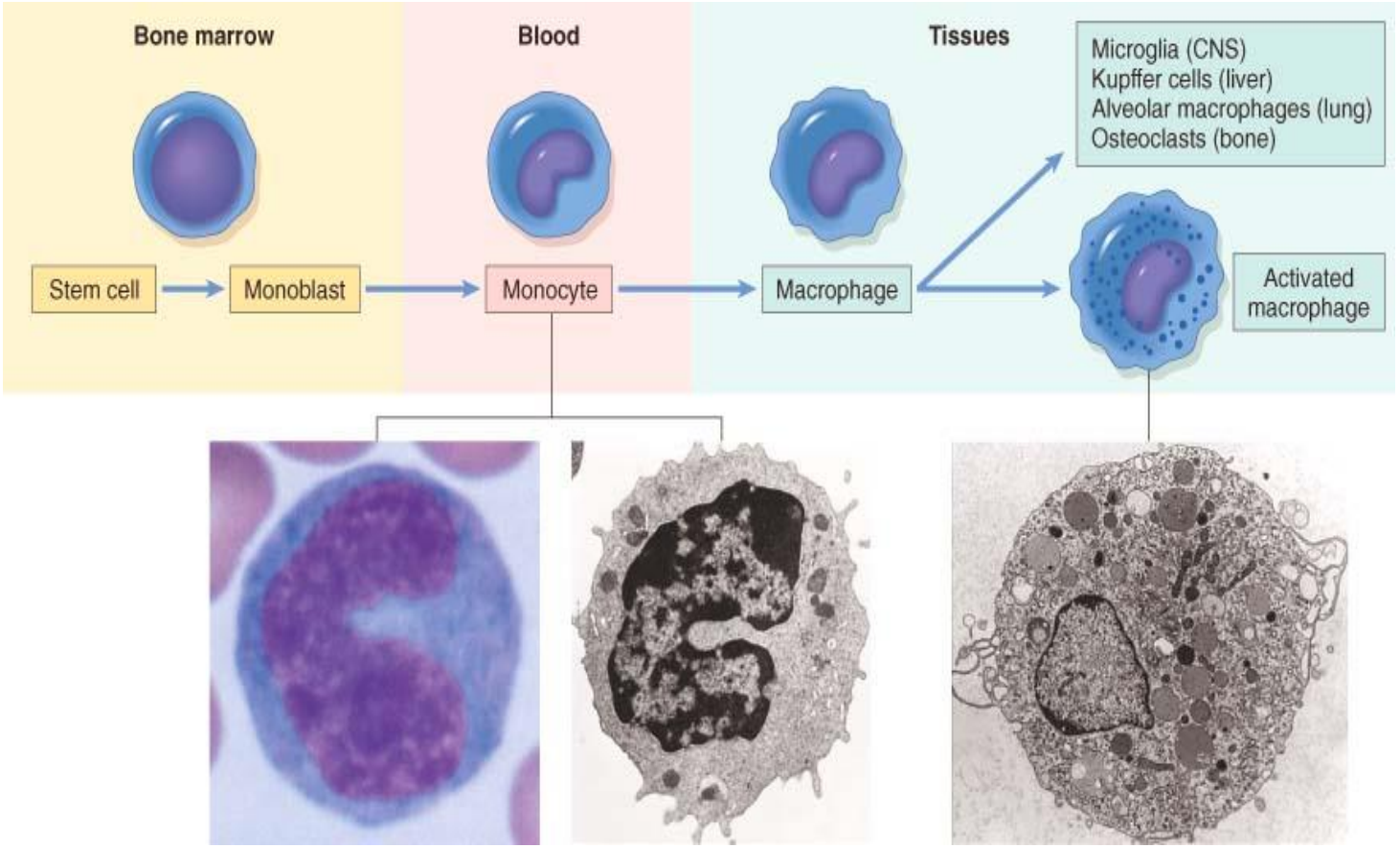
COMPOSITION OF GRANULOMA

1. Epithelioid cells
2. Multinucleate giant cells
3. Lymphoid cells
4. Necrosis
5. Fibrosis

1.Epithelioid cells

- So called because of their **epithelial cell-like appearance.**
- They are **modified macrophages** which are somewhat elongated cells having slipper-shaped nucleus.
- The nuclear chromatin of these cells is **vesicular** and lightly-staining
- The **cytoplasm is abundant, pale-staining with hazy outlines**
- Epithelioid cells are **weakly phagocytic.**



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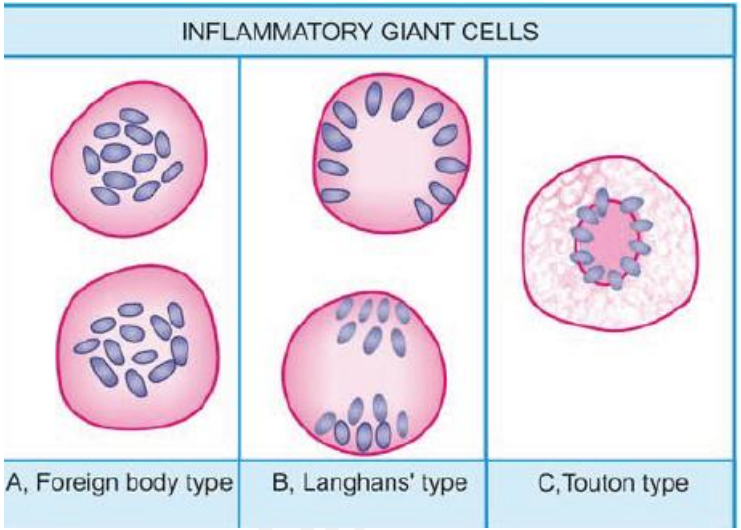
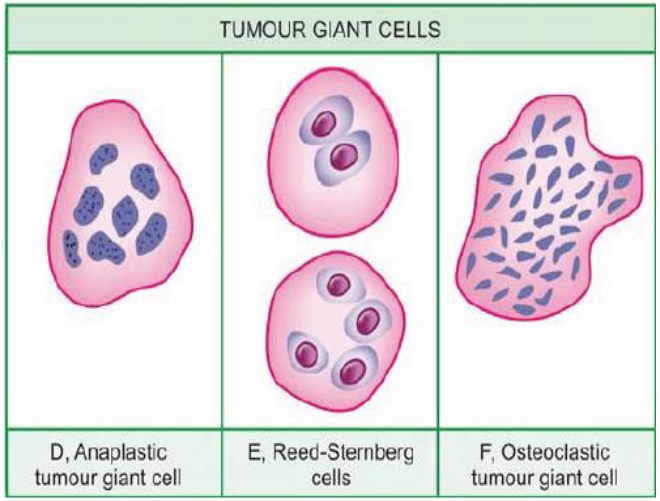
2. Multinucleate giant cells

- Formed by **fusion of adjacent epithelioid cells**
- may have **20 or more nuclei.**
- Like epithelioid cells, these giant cells are weakly phagocytic but produce secretory products which help in removing the invading agents.

Types of Giant cells

- Foreign body giant cells
- Langhans' giant cells
- Trouton giant cells
- Giant cells in tumours



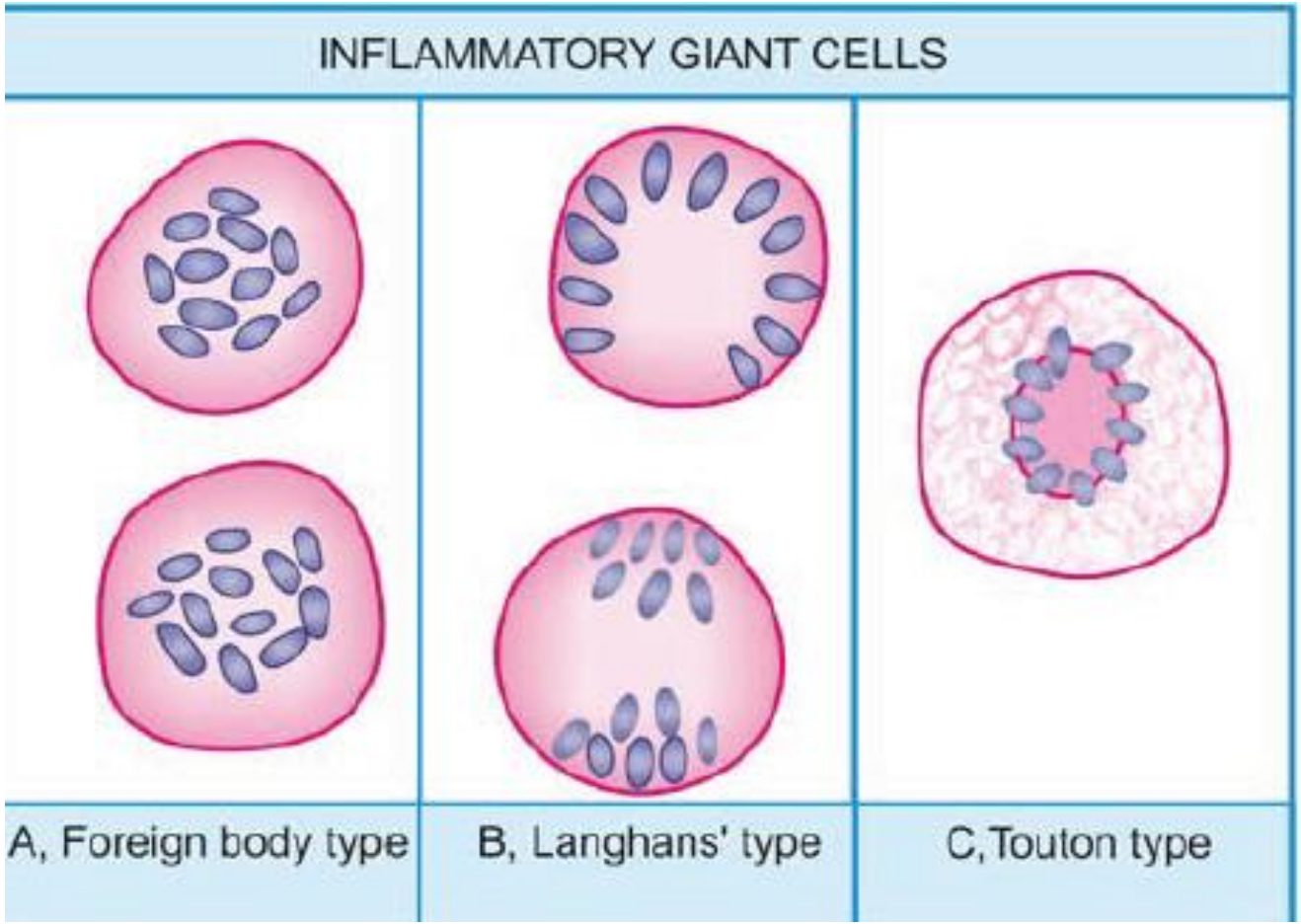


Foreign body giant cells

- Contain numerous nuclei (up to 100) which are uniform in size and shape and resemble the nuclei of macrophages.

- These nuclei are **scattered throughout the cytoplasm.**

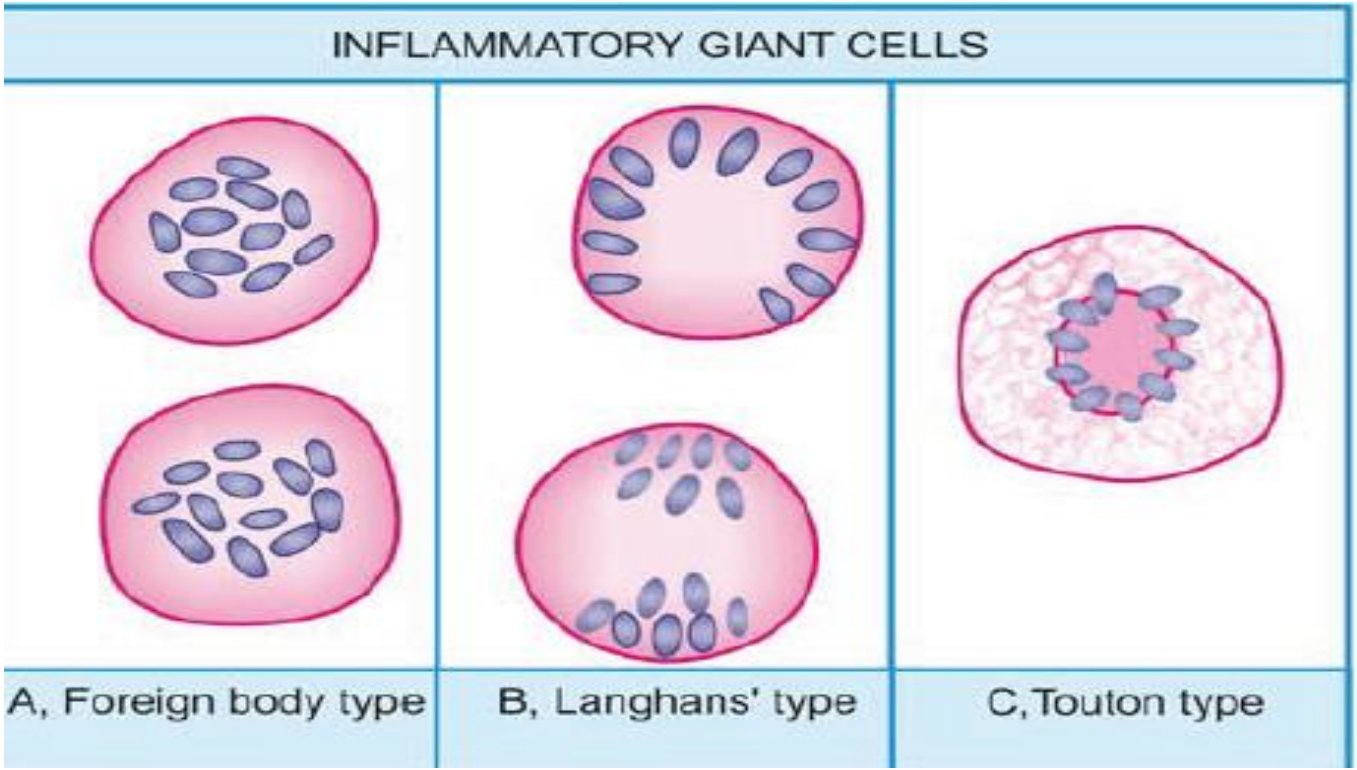
- Eg. chronic infective granulomas, leprosy and tuberculosis


INFLAMMATORY GIANT CELLS
A, Foreign body type
B, Langhans' type
C, Touton type

Langhans' giant cells

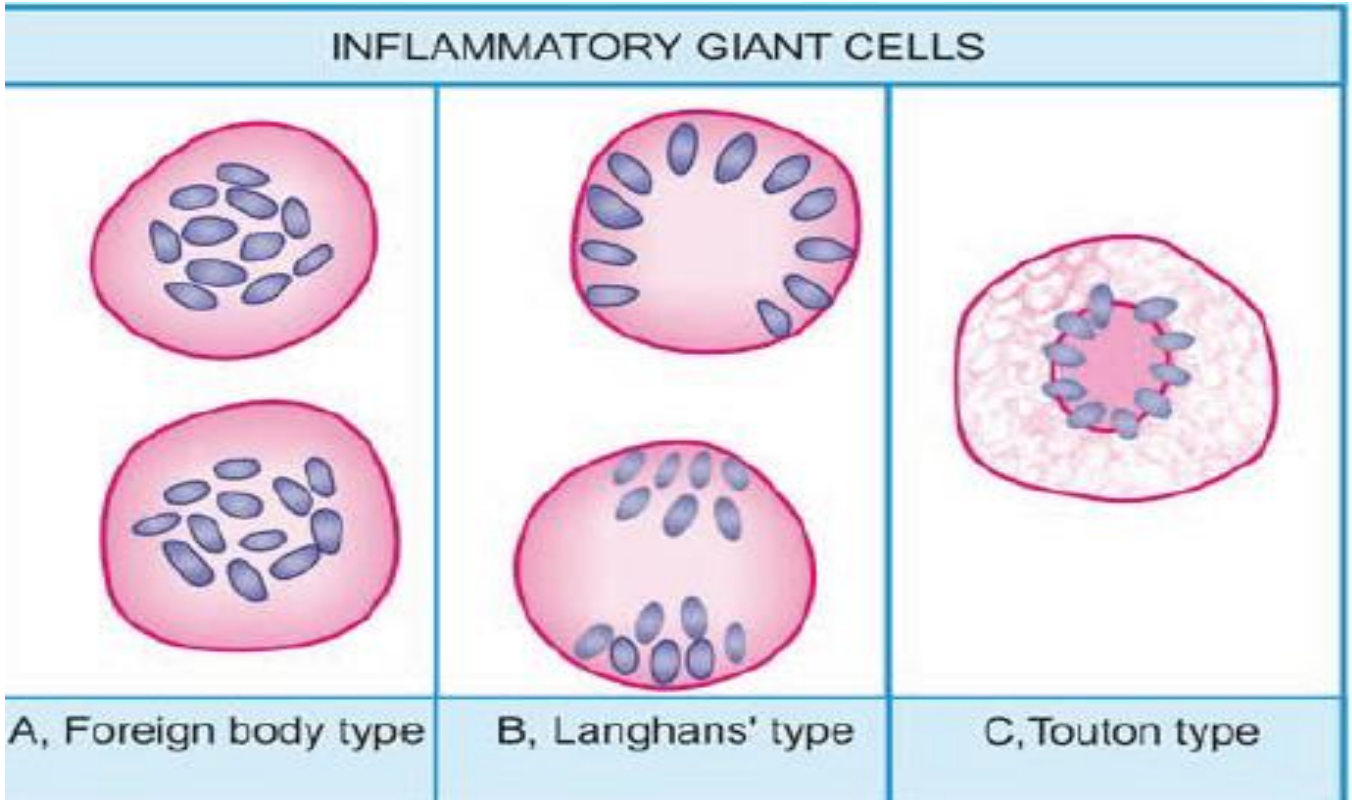
- Their nuclei are like the nuclei of macrophages and epithelioid cells
- Nuclei are arranged **either around the periphery in the form of horseshoe or ring, or are clustered at the two poles of the giant cell.**

- Eg. tuberculosis and sarcoidosis.


INFLAMMATORY GIANT CELLS
A, Foreign body type
B, Langhans' type
C, Touton type

Trouton giant cells

- These multinucleated cells have **vacuolated cytoplasm due to lipid content**
- e.g. in xanthoma



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Giant cells in tumours

Anaplastic cancer giant cells

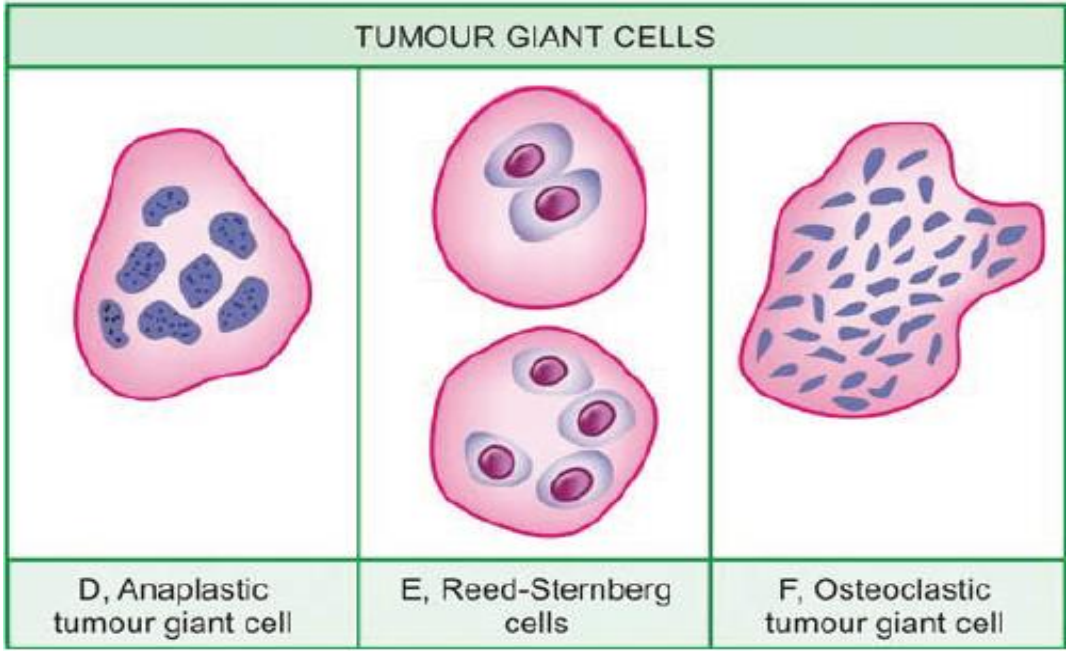
- These are larger, have numerous nuclei which are hyperchromatic and vary in size and shape.
- These giant cells are not derived from macrophages but are formed from neoplastic cells
- e.g. carcinoma of the liver, various soft tissue sarcomas etc

Reed-Sternberg cells

- These are also malignant tumour giant cells which are generally binucleate
- Eg. Hodgkin's lymphomas

Osteoclastic giant cells of bone tumour

- Eg. Giant cell tumour of the bones or osteoclastoma



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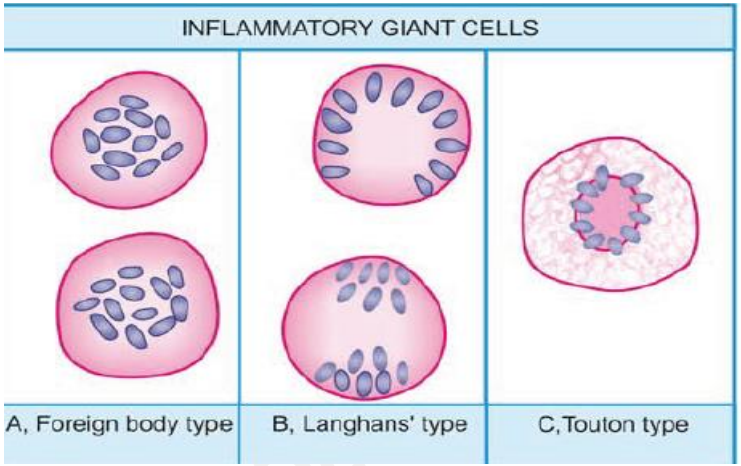
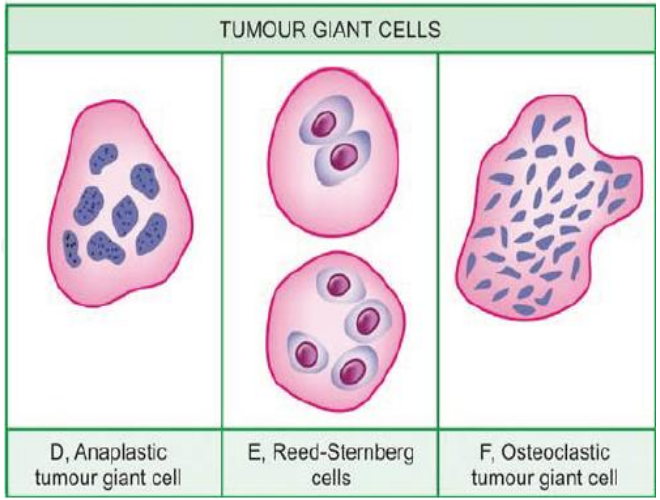




COMPOSITION OF GRANULOMA

1. Epithelioid cells
2. Multinucleate giant cells
3. Lymphoid cells
4. Necrosis
5. Fibrosis

3. Lymphoid cells

- As a cell-mediated immune reaction to antigen, the host response by lymphocytes is integral to composition of a granuloma.

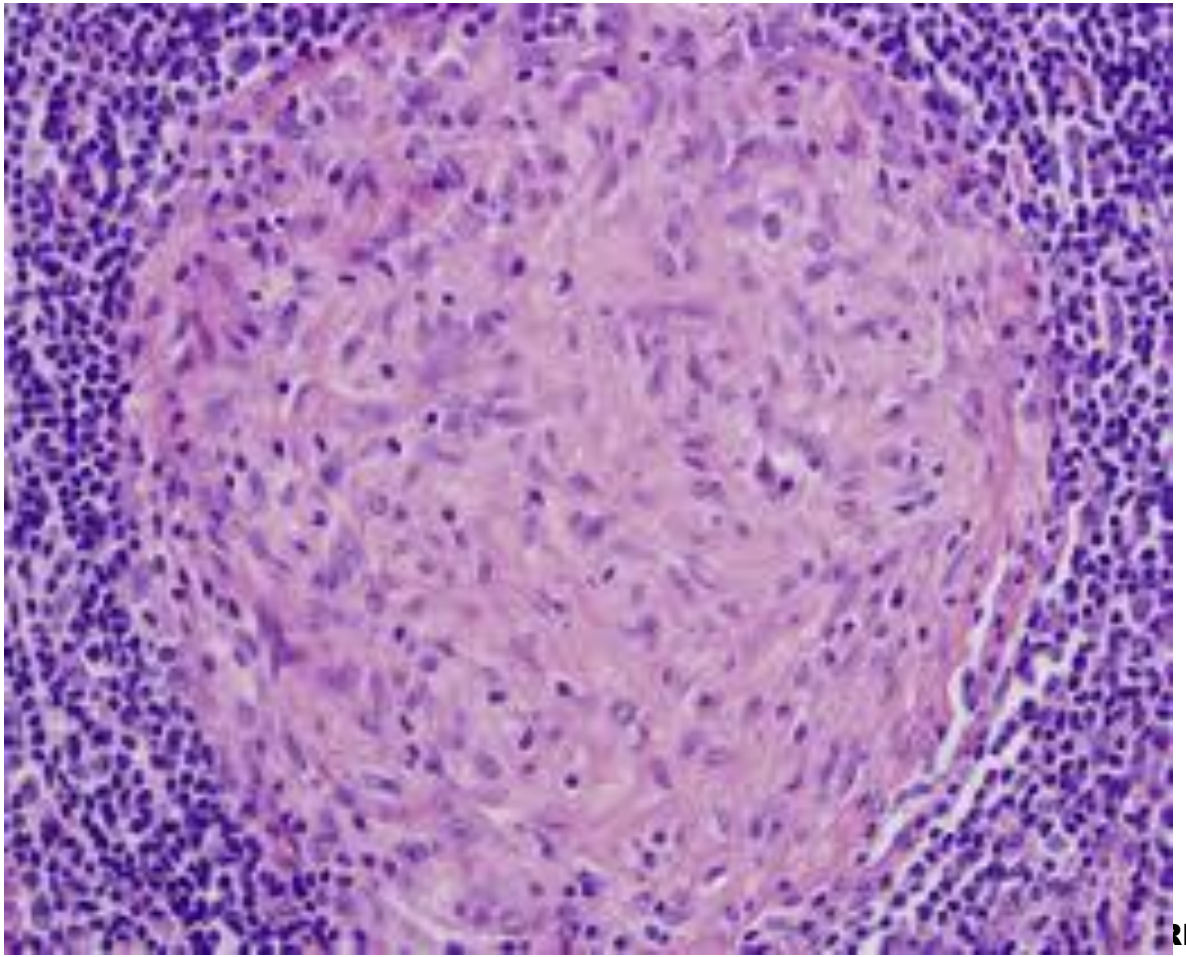
4. Necrosis

- Necrosis may be a feature of some granulomatous conditions

- e.g. central caseation necrosis in tuberculosis (cheese-like)

5. Fibrosis

- Fibrosis is a feature of healing by proliferating fibroblasts at the periphery of granuloma.



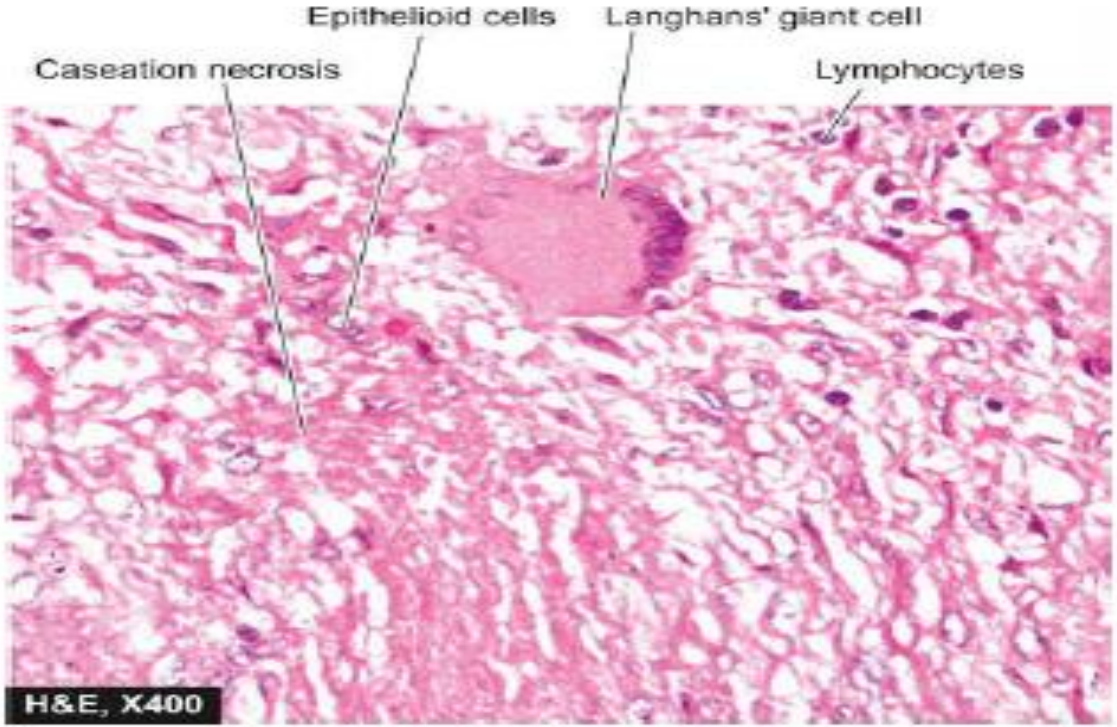
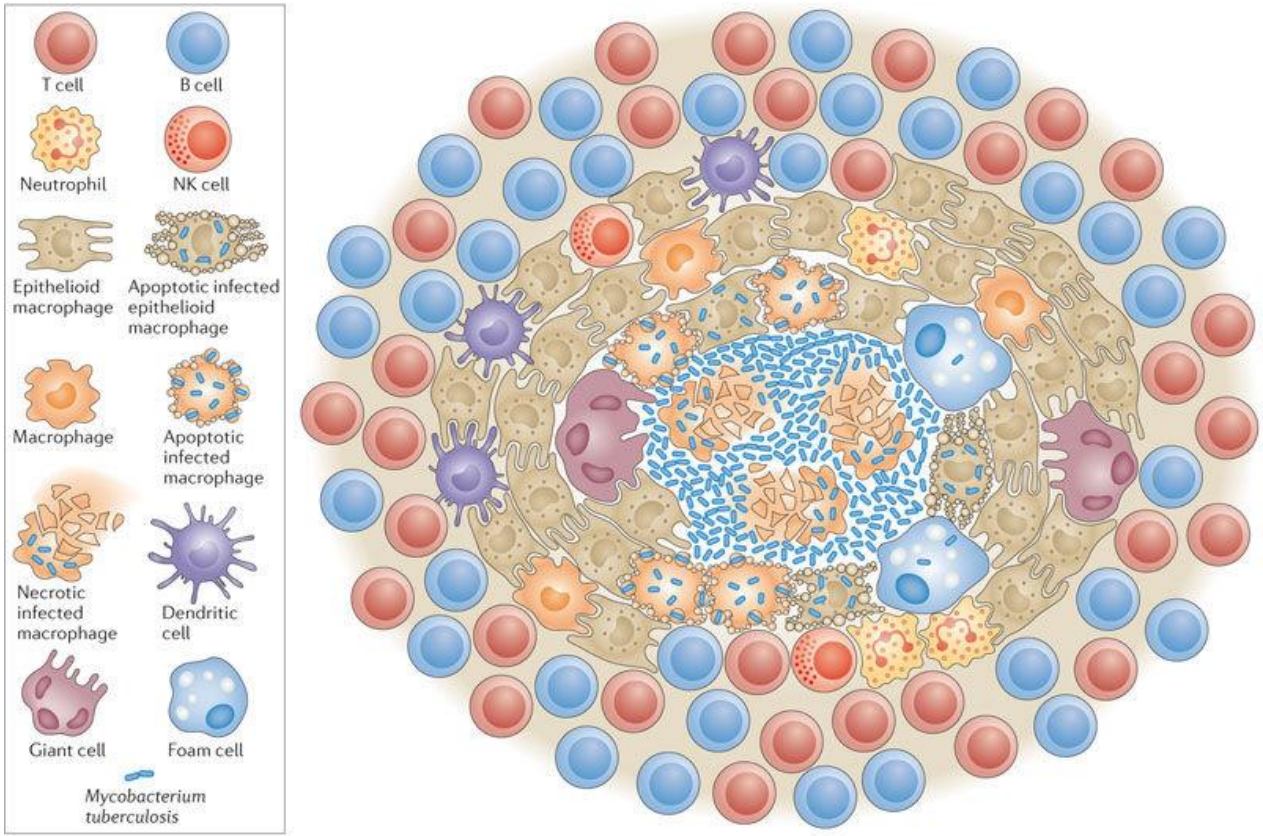


Figure 5.19 Morphology of a tubercle. There is central caseation necrosis, surrounded by elongated epithelioid cells having characteristic slipper-shaped nuclei, with interspersed Langhans' giant cells. Periphery shows lymphocytes.



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EXAMPLES OF GRANULOMATOUS INFLAMMATION

I.	BACTERIAL		
1.	*Tuberculosis**	*Mycobacterium tuberculosis*	Tuberculous granulomas with central caseation necrosis; acid-fast bacilli.
2.	*Leprosy**	*Mycobacterium leprae*	Foamy histiocytes with acid-fast bacilli (lepromatous); epithelioid cell granulomas (tuberculoid).
3.	*Syphilis**	*Treponema pallidum*	Gummas composed of histiocytes; plasma cell infiltration; central necrosis.
4.	*Granuloma inguinale (Donovanosis)*	*C. donovani (Donovan body)*	Anal and genital lesions; macrophages and neutrophils show Donovan bodies.
5.	*Brucellosis (Mediterranean fever)*	*Brucella abortus*	Dairy infection to humans; enlarged reticuloendothelial organs (lymph nodes, spleen, bone marrow); non-specific granulomas.
6.	*Cat scratch disease*	Coccobacillus	Lymphadenitis; reticuloendothelial hyperplasia; granulomas with central necrosis and neutrophils.
7.	*Tularaemia (Rabbit fever)*	*Francisella (Pasteurella) tularensis*	Necrosis and suppuration (acute); tubercles hard or with minute central necrosis (chronic).
8.	*Glanders*	*Actinobacillus mallei*	Infection from horses and mules; subcutaneous lesions and lymphadenitis; infective granulomas.

II.	FUNGAL		
1.	*Actinomycosis* (bacterial)*	*Actinomycetes israelii*	Cervicofacial, abdominal and thoracic lesions; granulomas and abscesses with draining sinuses; sulphur granules.
2.	*Blastomycosis*	*Blastomyces dermatitidis*	Cutaneous, systemic and lung lesions; suppuration; ulceration and granulomas.
3.	*Cryptococcosis*	*Cryptococcus neoformans*	Meninges, lungs and systemic distribution; organism yeast-like with clear capsule.
4.	*Coccidioidomycosis*	*Coccidioides immitis*	Meninges, lungs and systemic distribution; granulomas and abscesses; organism cyst containing endospores.
III.	PARASITIC		
	Schistosomiasis (Bilharziasis)	*Schistosoma mansoni, haematobium, japonicum*	Eggs and granulomas in gut, liver, lung; schistosome pigment; eosinophils in blood and tissue.

IV.	MISCELLANEOUS		
1.	*Sarcoidosis**	Unknown	Non-caseating granulomas (hard tubercles); asteroid and Schaumann bodies in giant cells.
2.	*Crohn's disease (Regional enteritis)*	Unknown ? Bacteria, ?? Viruses	Transmural chronic inflammatory infiltrates; non-caseating sarcoid-like granulomas.
3.	*Silicosis*	Silica dust	Lung lesions, fibrocollagenous nodules.
4.	*Berylliosis*	Metallic beryllium	Sarcoid-like granulomas in lungs; fibrosis; inclusions in giant cells (asteroids, Schaumann bodies, crystals).
5.	*Foreign body granulomas*	Talc, suture, oils, wood splinter etc.	Non-caseating granulomas with foreign body giant cells; demonstration of foreign body.

FEATURE	ACUTE INFLAMMATION	CHRONIC INFLAMMATION
1. *Onset and Duration*	• Within short time • Lasts for short duration	• After delay • Lasts longer
2. *Cardinal Signs*	Invariably present	Generally imperceptible
3. *Pathogenesis*	• Vascular events: haemodynamic changes, increased vascular permeability) • Cellular events: exudation of leucocytes, Phagocytosis • Role of chemical mediators and regulators	• Following acute inflammation • Recurrent attacks of acute inflammation • Chronic inflammation from beginning
4. *Main Inflammatory Cells*	• Neutrophils • Eosinophils • Lymphomononuclear cells (late) • Pus cells	• Lymphocytes • Plasma cells • Monocytes/macrophages (epithelioid cells in granulomas) • Giant cells (foreign body, Langhans')
5. *Plasma Exudation*	Present	May or may not be present
6. *Systemic Effects*	• Fever: high grade • Leucocytosis (neutropphilic, eosinophilic) • Lymphadenitis-lymphangiitis • Septic shock (in severe acute infection)	• Fever: mild • Leucocytosis (lymphocytic, monocytic) • Lymphadenitis-lymphangiitis • Raised ESR • Anaemia • Amyloidosis (in long-term cases)
7. *Main morphology*	• Abscesses (suppuration) • Ulcers • Through blood (Bacteraemia, septicaemia, pyaemia)	• Chronic non-specific inflammation (infectious, others) • Granulomatous inflammation (tuberculosis, leprosy, sarcoidosis, syphilis, actinomycosis, Crohn's disease etc)
8. *Fate*	• Resolution • Healing (regeneration, fibrosis) • Chronicity	• Resolution • Healing (regeneration, fibrosis) • Dystrophic calcification
9. *Common Examples*	Pyogenic abscess, cellulitis, bacterial pneumonia, pyaemia	Granulation tissue, granulomatous inflammation (tuberculosis, leprosy etc), chronic osteomyelitis

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Thank you for being awake

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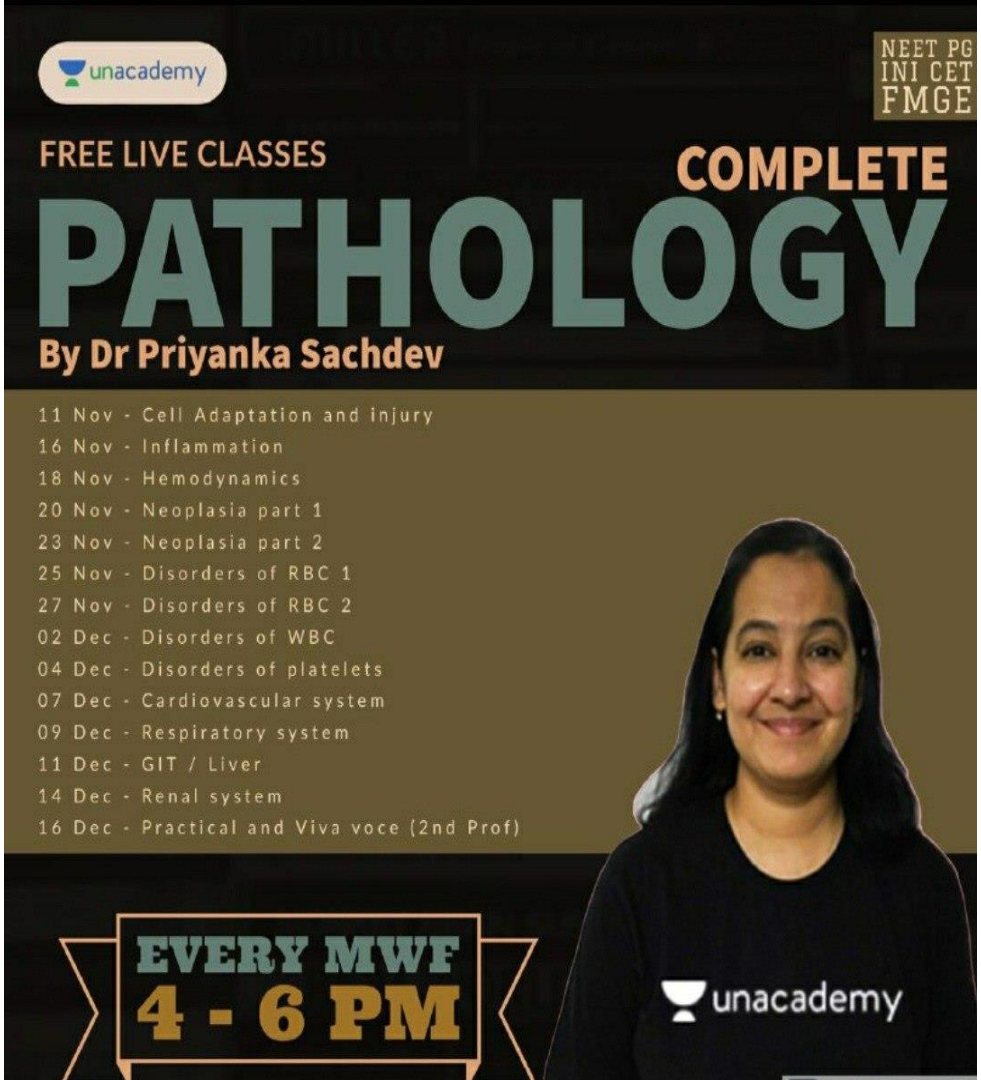
NEXT CLASS

- Every MWF (Monday , Wednesday , Friday)→PATHOLOGY

- Every TTS (Tuesday , Thursday , Saturday) → PHARMACOLOGY

YANKA SACHDEV



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- 19th Nov → THURSDAY → PHARMACOLOGY

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